A Platinum Open Access Journal for Organic Chemistry

Paper

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Morpholine catalyzed synthesis of novel 4*H*-chromene linked pyrazole - 1,2,3-triazole hybrids, screening for anticancer and antimicrobial effects

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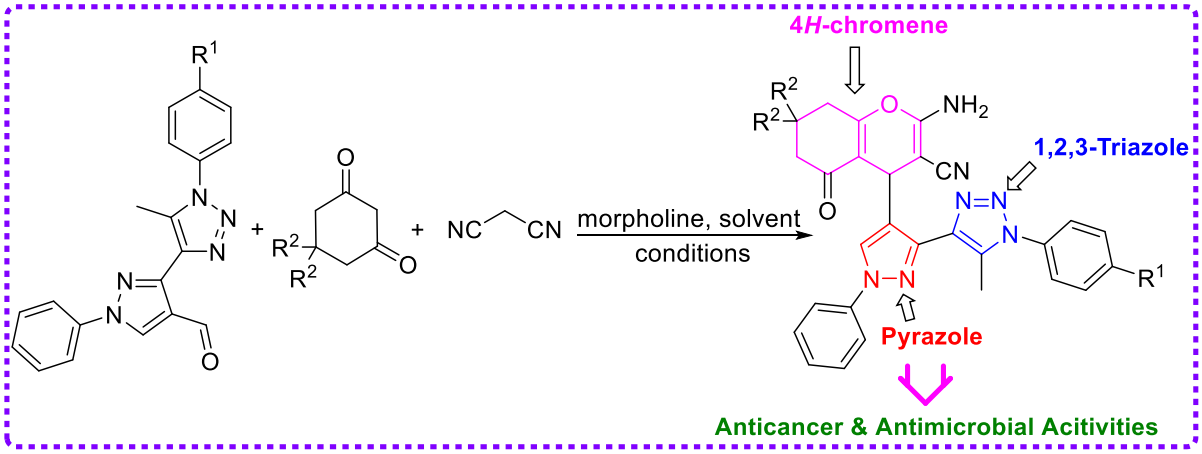
Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Abstract

A series of new 4*H*-chromene derivatives containing 1,2,3-triazole – pyrazole substituents were synthesized in good yields using easily available morpholine as a metal free catalyst in ethanol solvent. Advantages of this synthetic protocol include low cost, ready availability of catalyst, simple reaction conditions, minimal work up procedure, short reaction time, and high yields ranging 80 – 92%. The new compounds were tested for their in vitro cytotoxicity against MCF-7, HeLa and DU145 cell lines, and a 4-chlorophenyl substituted analogue presented potent activity with IC_{50} value of 6.67±0.39 µM, 8.44±0.32 µM and 9.38±0.29 µM against MCF-7, HeLa and DU-145 respectively. Antimicrobial screening of these new compounds garnered very good results as indicated by zone of inhibition and promising MIC values against bacterial and fungal strains. Molecular docking study of the most active compound against EGFR, DNA gyrase and Lanosterol 14-alpha demethylase revealed notable binding affinity values and important binding interactions.



Keywords: Antimicrobial agents, 4*H*-chromene, cytotoxicity, morpholine, pyrazole, 1,2,3-triazole

Cite as *Arkivoc* **2025** (5) 202512365

DOI: https://doi.org/10.24820/ark.5550190.p012.365

Introduction

One-pot multi-component reactions (MCRs) are a significant method for minimizing environmental pollution, energy consumption, reaction duration, and the amounts of starting materials in organic synthesis which aims to realize the principles of green chemistry. From a literature survey, the benzopyran derivative 4*H*-chromene-3-carbonitrile can be constructed by one pot three component tandem reaction of aldehyde, malononitrile and 1,3-dicabonyls containing enolizable C-H functional group in presence of different catalysts such as 2,2,2-trifluoroethanol (TFE),[1] biguanide-Functionalized Fe_3O_4/SiO_2 magnetic nano particles,[2] $RuBr_2(PPh_3)_4$,[3] p-dimethylaminopyridine (DMAP),[4] thiourea dioxide,[5] tetra butylammonium fluoride,[6] and piperidine[7] under microwave irradiation. For accomplishment of such a one pot multicomponent reaction, herein we describe use of the easily available, low cost and environmentally friendly morpholine as catalyst, which leads to easy work up procedure, short reaction time, and high yield.[8]

4*H*-Chromenes are an important class of heterocyclic molecules and are prominent core in many naturally occurring products.[9] Chromene constitutes the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins.[10] Natural and synthetic chromene derivatives possess a wide variety of pharmacological activities such as antitumor,[11] antivascular,[12] antimicrobial,[13] antioxidant,[14] TNF-α inhibitor,[15] antifungal,[16] anticoagulant,[17] anti-spasmolytic,[18] estrogenic,[19] antiviral,[20] anti-helminthic,[21] anticancer,[22] anti-HIV,[23] antitubercular,[24] anti-inflammatory,[25,26] herbicidal,[27] analgesic,[28] and anticonvulsant activity.[29] A key feature is that the lipophilic nature of the benzopyran derivatives helps to cross the cell membrane easily.[30]

As important constituents of heterocyclic compounds, pyrazoles exhibit a wide range of biological activities and have pharmaceutical applications in a number of specialized domains. These domains include, but are not limited to anti-cancer,[31] antimicrobial,[32] and anti-inflammatory activities.[33,34,35] 1,2,3-Triazole derivatives became of medicinal interest due to numerous applications as antimicrobial,[36] anti-diabetic,[37] anti-cancer,[38] anti-inflammatory[39] and antitubercular[40] agents.

Treating infections caused by microorganisms has become a great medical challenge to the world. According to World Health Assembly,[41] abuse and repeated use of antibiotics, has led to many microorganisms developing resistance to the antibiotics, thereby exacerbating this medical challenge. To overcome the issues, many pharmaceutical research groups focused on the development of new and effective antimicrobial agents.[42] In extension to our previously published work[43] and biological significance of 4*H*-chromene, pyrazole and 1,2,3-triazole nuclei and their hybrids, it attracted us to design new molecular hybrids containing 4*H*-chromene, pyrazole and 1,2,3-triazole analogues,[44,45] and evaluate their biological activities such as anticancer and antimicrobial properties.

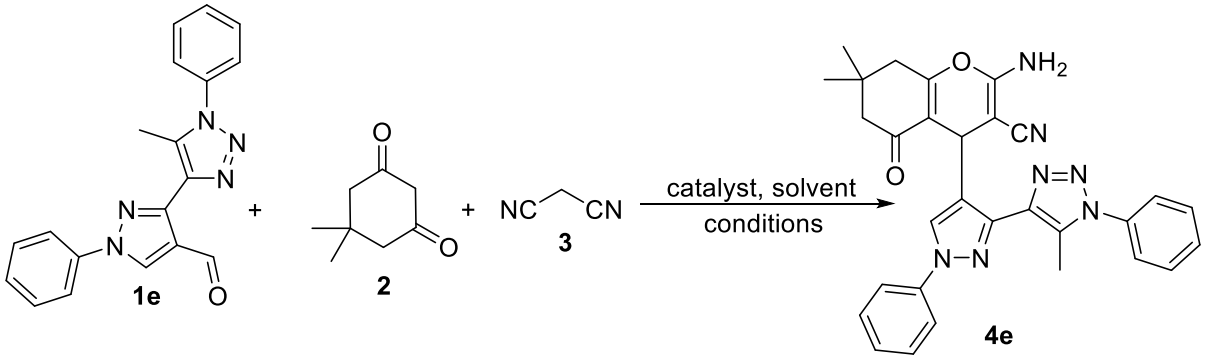
Results and Discussion

Motivated by the cheap and easy availability of morpholine, a small, focused library of new 4*H*-chromene-based pyrazole – 1,2,3-triazole hybrids **4a-n** was synthesized using a three-component condensation reaction involving aldehyde, malononitrile, and dimedone, catalyzed by morpholine in ethanol at ambient temperature. A preliminary study on preparation of compound **4e** involved an in-depth investigation of this synthetic route (Scheme 1, Table 1). Reactions conducted at room temperature in water with each of three distinct catalysts (DBU, piperazine, and morpholine) yielded no intended product due to the insolubility of the reactants. Under reflux conditions, the desired compound was produced in trace amounts. By the use of an ethanol and water mixture (1:1, v/v) at room temperature, a significant quantity of product was obtained, accompanied by some

contaminants. However, we attained superior yield using ethanol as the sole solvent, combined with morpholine at ambient temperature. Moreover, no significant enhancement in yield was noted when the reaction was conducted under reflux with morpholine. This study compared the efficacy of morpholine with DBU and piperazine, both of which have been identified as catalysts for the synthesis of pyran rings in multicomponent processes. However, the use of morpholine as a catalyst resulted in increased yields. One report indicated that 4*H*-chromene-3-carbonitriles were obtained in high yields from reactions conducted under catalyst-free conditions in ethanol;[46] however, in our hands, reactions conducted in the absence of morpholine did not afford the desired products in acceptable yields.

The probable mechanism[47] for the formation of the 4*H*-chromene ring facilitated by morpholine is illustrated in Scheme 2. The activated CH_2 group of dimedone **I** was deprotonated by morpholine to form carbanion compound **II**. The carbanion compound **II** was involved in an addition reaction with the carbonyl group of the aldehyde to afford intermediate **III**. Subsequent proton transfer led to formation of intermediate **IV** followed by elimination of water to give intermediate **V**. Finally, Michael addition of malononitrile anion to intermediate **V** followed by cyclization provided the target 4*H*-chromene ring **VI**.

A possible alternative mechanism,[8] shown in Scheme 3, could be initiated by deprotonation of the activated CH_2 group of malononitrile **VIII** to generate carbanion intermediate **IX**. Attack of carbanion of **IX** on the carbonyl group of the aldehyde gave intermediate **X**, which was transformed to intermediate **XI** by protonation. Elimination of a water molecule from **XI** formed an olefine intermediate **XII**. Attack of dimedone carbanion **II** on electrophilic carbon of **XII** gave intermediate **XIII**. Intramolecular cyclization afforded intermediate **VI**. Finally, tautomerization of intermediate **VI** provided the target 4H-chromene ring **VI**.

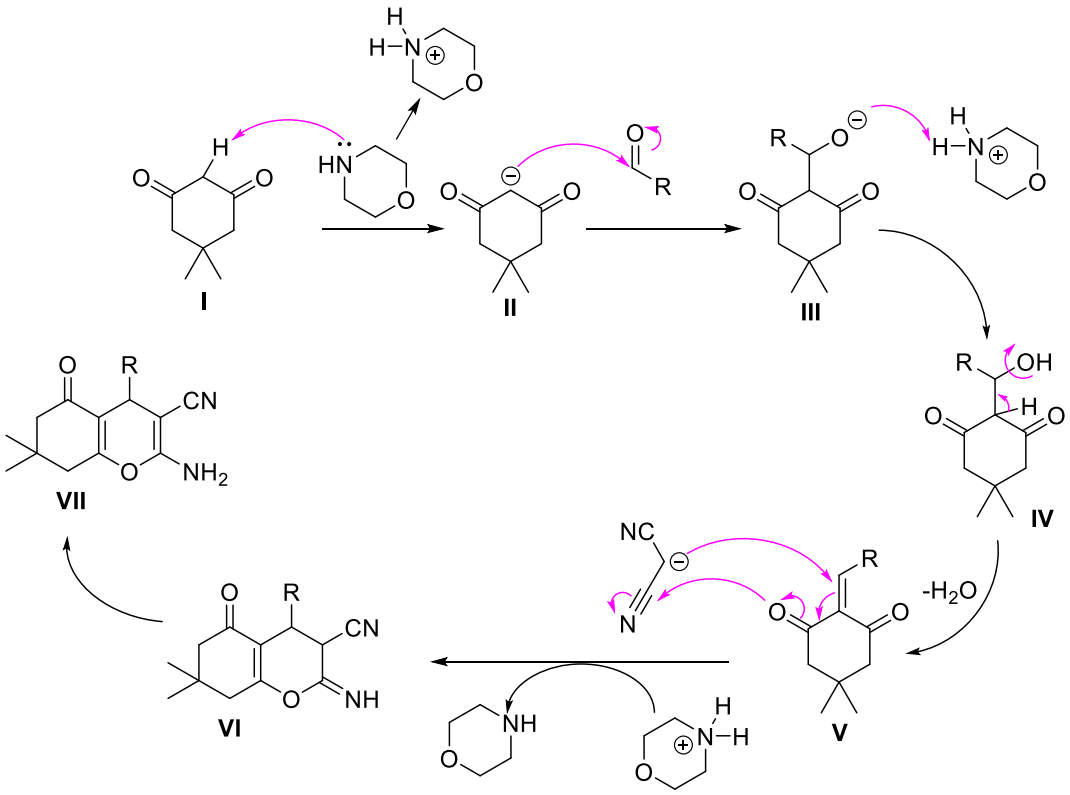


Scheme 1. Optimization of reaction protocol for synthesis of 4*H*-chromene – pyrazole – 1,2,3-hybrid **4e**.

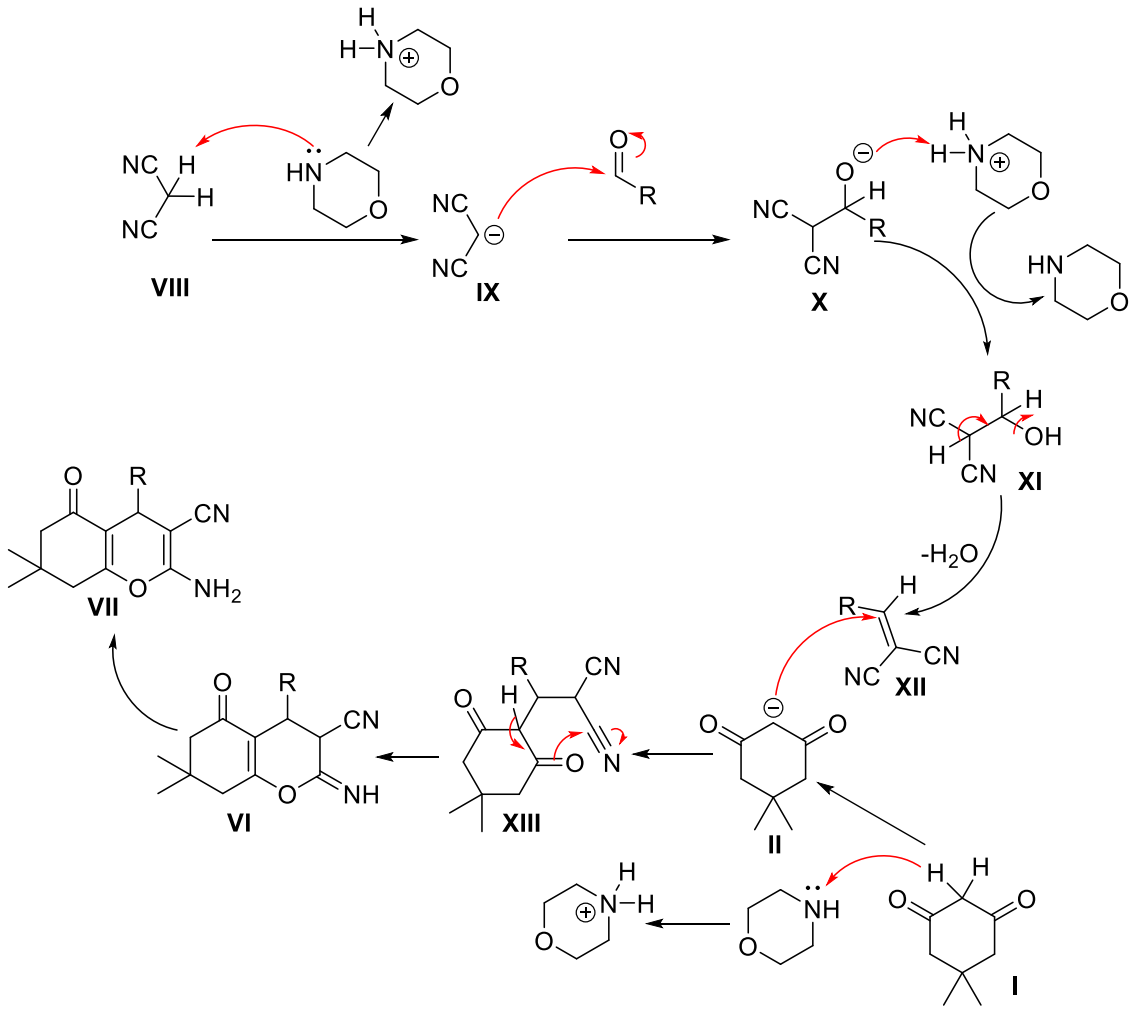
Table 1. Optimization of reaction conditions for synthesis of compound **4e**

S.No	Solvent	Temp	Catalyst	Time	Yield
1	H_2O	rt	DBU	8 h	No product
2	H_2O	rt	piperazine	8 h	No product
3	H_2O	rt	morpholine	8 h	No product
4	H_2O	reflux	DBU	8 h	Traces
5	H_2O	reflux	piperazine	8 h	Traces
6	H_2O	reflux	morpholine	8 h	No product
7	EtOH:Water	rt	DBU	3 h	54%
8	EtOH:Water	rt	piperazine	2 h	56%
9	EtOH:Water	rt	morpholine	2 h	55%
10	EtOH:Water	reflux	DBU	2 h	65%

11	EtOH:Water	reflux	piperazine	2 h	72%
12	EtOH:Water	reflux	morpholine	2 h	76%
13	EtOH	rt	DBU	2 h	59%
14	EtOH	rt	piperazine	75 min	84%
15	EtOH	rt	morpholine	80 min	92%
16	EtOH	reflux	DBU	2 h	62%
17	EtOH	reflux	piperazine	75 min	88%
18	EtOH	reflux	morpholine	80 min	92%

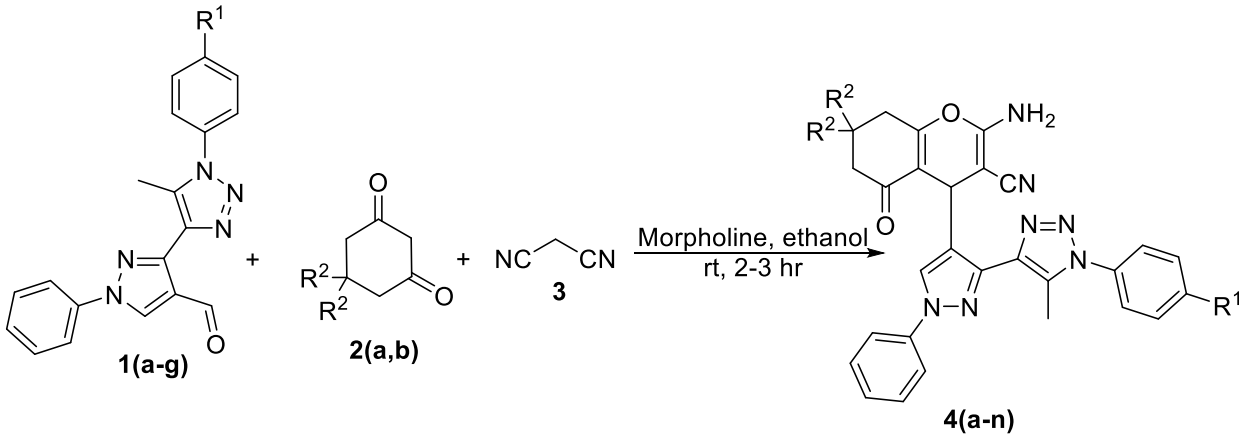


Scheme 2. Plausible mechanism for formation of 4*H*-chromene ring via initial formation of dimedone anion.



Scheme 3. Plausible alternative mechanism via initial formation of malononitrile anion.

Based on the optimized conditions, a series of reactions were carried out under similar conditions to provide the desired compounds **4(a-n)** as illustrated in Scheme 4. To achieve our target molecules **4(a-n),** we synthesized precursor molecules **1(a-g),** as per the reported protocol in our previous work using various substituted amines as precursors.[43] These molecules, on treatment with different 3-dicarbonyl compounds **2(a-b)** and malononitrile **3** in presence of morpholine in ethanol at room temperature, gave the titled compounds **4(a-n)** and the results are depicted in Table 2.



Scheme 4. Synthetic route for the title compounds **(4a-n)**.

Table 2. Physical data from the desired compounds **4(a-n)**.

Entry	Compound	R^1	R^2	Time (min)	M.p. (°C)	Yield (%)
1	**4a**	CH_3	CH_3	70	196-198	90
2	**4b**	Cl	CH_3	60	200-202	89
3	**4c**	F	CH_3	65	206-208	91
4	**4d**	OCH_3	CH_3	60	190-192	89
5	**4e**	H	CH_3	75	188-190	92
6	**4f**	NO_2	CH_3	80	180-182	88
7	**4g**	Br	CH_3	65	194-196	84
8	**4h**	CH_3	H	70	198-200	84
9	**4i**	Cl	H	60	202-204	89
10	**4j**	F	H	65	204-206	85
11	**4k**	OCH_3	H	60	194-196	84
12	**4l**	H	H	75	186-188	82
13	**4m**	NO_2	H	80	182-184	80
14	**4n**	Br	H	65	196-198	83

Cytotoxicity

The newly produced analogues **4a-n** were tested for their anticancer activity *in vitro* using three different cancer cell lines: MCF-7 (breast cancer), HeLa (cervical cancer), and DU-145 (prostate cancer). Using doxorubicin as a reference substance, the MTT test was used to conduct the study. Table 3 exhibited the experimental results, which were calculated as IC_{50} values. Depending on the cell lines tested, these compounds showed mild, moderate, or strong activity. The activities of compounds **4f** and **4i** were the most promising results. A structure activity relationship (SAR) analysis was carried out to determine the effects of substituents on biological activity. The 4-chlorophenyl substituted compound **4i** featuring electron withdrawing function presented potent activity with IC_{50} values of **6.67±0.39 µM**, **8.44±0.32 µM** and **9.38±0.29 µM** against MCF-7, HeLa and DU-145 respectively. Compound **4f**, containing 4-nitrophenyl function featuring electron withdrawing group and methyl groups presented on chromene ring displayed potent activity with with IC_{50} values of **8.32±0.62 µM** (MCF-7), **9.87±0.33 µM** (HeLa) and **12.40±0.60 µM** (DU-145). These two molecules' activity was very much comparable to the IC_{50} value of Doxorubicin *viz*. **8.48±0.28 µM** (MCF-7), **9.33±0.22 µM** (HeLa) and **9.64±0.29 µM** (DU-145).

Table 3 IC_{50} values (in µM) for compounds **4a-n**

Entry	IC_{50} value (µM)			
	MCF-7	HeLa	DU-145	HEK-293
4a	14.12±0.71	15.52±0.90	17.78±0.75	> 100
4b	22.75±0.73	21.71±0.48	23.58±1.14	98.23±3.22
4c	20.83±3.23	19.95±1.40	22.83±1.64	94.85±2.96
4d	15.12±0.69	17.89±0.38	15.78±0.73	> 100
4e	20.12±1.02	12.75±0.97	28.37±1.92	> 100
4f	8.32±0.62	9.87±0.33	12.40±0.60	97.44±4.25
4g	24.17±1.09	16.56±1.63	33.82±2.69	> 100
4h	25.45±2.07	25.0±2.42	37.84±3.41	> 100

4i	6.67±0.39	8.44±0.32	9.38±0.29	> 100
4j	19.90±0.51	10.31±0.30	22.61±1.53	92.84±3.48
4k	15.18±0.56	16.22±1.57	18.09±1.63	> 100
4l	36.13±4.56	35.91±0.93	33.81±0.80	99.73±3.20
4m	20.22±2.51	19.68±0.10	18.67±0.51	83.68±3.11
4n	14.12±0.76	15.52±0.38	16.78±0.73	86.61±2.81
Doxorubicin	8.48±0.28	9.33±0.22	9.64±0.29	Not tested

Presence of a bulky bromo function on compound **4n** diminished the activity slightly to IC_{50} values of 14.12±0.76 µM (MCF-7), 15.52±0.38 µM (HeLa) and 16.78±0.73 µM (DU-145). Presence of methyl group featuring electron donating function on compound **4a** showed little change in activity in comparison to compound **4n**. Slight decrease in activity was observed when methoxy group, an electron donating function, was present on compound **4d**. Similar pattern was observed with **4k** in which methoxy group was present. The compounds' activity can be ascribed to the presence of 4*H*-chromene, pyrazole, and 1,2,3-triazole rings, which function as pharmacophores.

Antimicrobial Activity

All the newly synthesized substances were examined for antimicrobial properties. Zones of inhibition (mm) and Minimum Inhibitory Concentrations (MICs) for all synthesized compounds against the four bacterial strains viz *S. aureus*, *B. cereus*, *E. coli*, and *P. aeruginosa*, and two fungal strains, *Aspergillus* and *Candida albicans*, were determined. Results are summarized in Tables 4 & 5.

Table 4. Inhibition Zone (mm) of compounds (1 mg/ml) against bacterial and fungal strains.

Entry	*S. aureus*	*B. cereus*	*E. coli*	*P. aeruginosa*	*Aspergillus*	*C. albicans*
4a	19.1	21	18.2	19.4	20.2	19.4
4b	21.3	21.8	21.2	20.3	21.6	20.8
4c	17.6	18.2	18.9	19.2	19.8	19
4d	18.8	19.8	20.2	18.3	21.6	18.8
4e	18.4	19.6	18.6	19.1	20.2	19.7
4f	15.8	16.2	17.8	18.1	18.2	17.9
4g	14.4	17.8	18.3	18.8	14.8	16.4
4h	14.1	14.6	16.4	15.2	15.4	15.2
4i	22.3	22.7	23.3	22.8	23.6	23.6
4j	12.8	13.2	13.7	14.8	13.2	14.9
4k	12.2	12.4	12.4	12.9	13.4	13.8
4l	11.8	10.6	11.8	10.4	15.2	12.9
4m	10.6	9.7	11.2	12.1	13.8	12.6
4n	9.2	9.3	10.6	11.6	13.7	15.6
Ciprofloxacin (100 µg/ml)	24.2	23.5	25	24.6	-	-
Nystatin (100 µg/ml)	-	-	-	-	25	24.8

Table 5 MIC (µg/ml) of all synthesized compounds against bacterial and fungal strains

Entry	S. aureus	B. cereus	E. coli	P. aeruginosa	Aspergillus	C. albicans
4a	19.4	12.6	13.4	12.9	20.6	22.4
4b	16.4	10.8	11.5	10.6	19.8	20.9
4c	30.4	29.6	35.1	36.6	30.4	30.7
4d	20.7	14.4	13.6	13.8	21.5	21.6
4e	20.3	15.6	16.9	15.3	21.6	24.1
4f	28.2	34.8	29.2	32.9	31.6	32.2
4g	36.8	38.7	36.4	38.2	34.8	37.1
4h	33.4	37.2	36.1	35.3	41.8	41.2
4i	15.4	9.2	10.4	9.8	18.4	19.6
4j	41.6	45.1	49.2	47.6	33.2	36.8
4k	46.8	47.4	41.4	49.9	49.6	46.8
4l	41.6	41.2	49.3	47.9	52.6	52.8
4m	40.6	43.4	48.8	46.4	49.5	48.3
4n	38.8	40.3	39.6	41.1	47.6	49.6
Ciprofloxacin	15	9	10	9.6	-	-
Fluconazole	-	-	-	-	18	19.4

All of the compounds showed good inhibitory zones and MIC values against gram +ve, gram -ve, and fungal pathogens when compared to the reference substances ciprofloxacin and fluconazole. The tested compounds demonstrated remarkable antibacterial effectiveness against bacterial and fungal strains, comparable to the grade medications Ciprofloxacin and Fluconazole, respectively. Compounds **4i**, **4b**, **4a**, and **4e** dramatically reduced microbial growth as compared to all other chemicals evaluated in this series. These substances had lower MIC values and broader inhibition zones. The most efficient anti-bacterial and anti-fungal chemicals, according to the research, are **4i** and **4b**. Furthermore, **4a** had shown good and **4e** demonstrated moderate antibacterial and antifungal activity, and the remaining compounds demonstrated negligible activity. Overall, the series of compounds with gem-dimethyl substitution at C7 position of chromene ring presented better antimicrobial activities compared to the other series without dimethyl groups.

Docking studies

To get an insight on the binding interactions, we performed computational screening of the most potent ligand **4i** against the crystal structure of Epidermal Growth Factor Receptor (EGFR) (PDB ID: 2J6M),[48] DNA gyrase subunit B (PDB ID: 2XCT)[49] and Lanosterol 14-alpha demethylase (PDB ID: 4WMZ).[50] The docking scores of ligand **4i** were found to be respectively of -10.2 kcal/mol; -9.1 kal/mol and-10.0 kcal/mol which could be compared to the binding affinity of -9.2 kcal/mol exhibited by ligand AEE788, 7.0 kcal/mol for ciprofloxacin and -7.4 kcal/mol for fluconazole. The full description of the docking study, including figures showing the binding interactions are reported in the supplementary material associated to this manuscript.

Conclusions

Morpholine is an efficient base/catalyst, providing another useful method to synthesize 2-amino-4-aryl-4H-chromene-3-carbonitriles and analogs by condensation of aldehydes, malononitrile and cyclic 1,3-dicarbonyl compounds. This synthetic protocol has some advantages which include low cost and easy availability of morpholine, simple reaction conditions, minimal work up procedure, short reaction time, and high yield. A set of new 2-amino-4-(pyrazol-4-yl)-4H-chromene-3-carbonitriles was synthesized and screened for in vitro cytotoxicity and antimicrobial activity. The compounds generally showed some cytotoxicity, with the most promising compounds being **4i** with IC_{50} values of 6.67±0.39 µM, 8.44±0.32 µM and 9.38±0.29 µM against MCF-7, HeLa and DU-145, respectively, and **4f** with IC_{50} values of 8.32±0.62 µM (MCF-7), 9.87±0.33 µM (HeLa) and 12.40±0.60 µM (DU-145). The compounds also generally showed some antimicrobial activity; the most promising compound was again **4i** with MIC values of 15.4 (S. aureus), 9.2 (B. cereus), 10.4 (E. coli), 9.8 (P. aeruginosa), 18.4 (Aspergillus), and 19.6 (C. albicans) ug/mL, respectively. Molecular docking studies of the best compound **4i** against EGFR, DNA gyrase and Lanosterol 14-alpha demethylase revealed notable binding affinity values and important binding interactions. Hence, the newly synthesized 4H-chromene based pyrazole – 1,2,3-triazole hybrids could be considered as starting points for anticancer and antimicrobial drug discovery efforts.

Experimental Section

General. Reagents and solvents were purchased from Sigma Aldrich and other commercial suppliers. Progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light. Column chromatography was performed on silica gel (60–120 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker AVANCE-400 spectrometer at 400 and 100 MHz respectively, using $CDCl_3$ and DMSO solvents. Proton chemical shifts (δ) are relative to tetramethyl silane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiple). Coupling constants (J) are given in Hertz. Melting points were determined using a Stuart SMP3 melting point apparatus and are uncorrected.

General procedure for synthesis of compounds 4(a-n). A mixture of aldehyde **1** (1 mmol), dimedone **2** (1 mmol), malononitrile **3**(1.3 mmol) and morpholine (0.1mmol) in ethanol (20 ml) was stirred at rt for 60 – 80 minutes. The reaction mixture was poured into fresh crushed ice. The solid obtained was filtered and washed with excess of water and dried. The crude was purified by column chromatography by using n-hexane and ethyl acetate (4:1 v/v) as eluent, which gave the compounds **4(a-n).**

2-Amino-7,7-dimethyl-4-(3-(5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4a). Off-white solid. Yield: 90%. m.p.: 196 – 198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.36 (s, 4H), 7.26 (d, *J* = 12.9 Hz, 1H), 4.85 (s, 1H), 4.46 (s, 2H), 2.53 (s, 3H), 2.46 (s, 3H), 2.33 – 2.22 (m, 2H), 2.19 (s, 2H), 1.06 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 162.3, 158.4, 143.2, 139.9, 139.6, 139.0, 133.9, 132.3, 130.1, 129.3, 127.9, 126.2, 124.9, 123.6, 119.4, 118.7, 111.9, 61.3, 50.9, 40.6, 31.9, 28.6, 27.7, 26.7, 21.2, 10.0. ESI – MS: m/z 532.25 $[M+H]^+$. CHN analysis calcd for $C_{31}H_{29}N_7O_2$: C, 70.04; H, 5.50; N, 18.44 %. Found: C, 70.00; H, 5.44; N, 18.40.

2-Amino-4-(3-(1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4b). Off-white solid. Yield: 89%. m.p.: 200 – 202 °C. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.41 (m, 4H), 7.29 (s, 1H), 4.89 (s, 1H), 4.44 (s, 2H), 2.57 (s, 3H), 2.40 (dd, *J* = 60.8, 17.5 Hz, 2H), 2.19 (d, *J* = 2.7 Hz, 2H), 1.07 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 172.2, 162.2, 158.3, 142.9, 139.8, 139.4, 135.5, 134.9, 132.2, 129.8, 129.3, 127.9, 126.3, 123.7, 118.8, 112.0, 61.5, 50.9, 40.7, 32.0, 28.7, 27.7, 26.6, 10.1. ESI – MS: m/z 552.22 $[M+H]^+$. CHN analysis calcd for $C_{30}H_{26}ClN_7O_2$: C, 65.27; H, 4.75; N, 17.76 %. Found: C, 65.23; H, 4.70; N, 17.71.

2-Amino-4-(3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c). Off-white solid. Yield: 91%. m.p.: 206 – 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.50 – 7.42 (m, 4H), 7.28 (d, *J* = 5.6 Hz, 3H), 4.89 (s, 1H), 4.44 (s, 2H), 2.55 (s, 3H), 2.41 (dd, *J* = 62.3, 17.2 Hz, 2H), 2.20 (s, 2H), 1.07 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 166.9, 163.6, 147.8, 144.5, 143.6, 137.2, 134.3, 132.3, 132.2, 131.8, 131.3, 131.0, 124.8, 123.0, 121.5, 121.3, 117.2, 63.2, 55.5, 36.8, 33.2, 32.9, 30.7, 14.6. ESI – MS: m/z 536.23 $[M+H]^+$. CHN analysis calcd for $C_{30}H_{26}FN_7O_2$: C, 67.28; H, 4.89; N, 18.31 %. Found: C, 67.24; H, 4.83; N, 18.27.

2-Amino-4-(3-(1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d). Off-white solid. Yield: 89%. m.p.: 190 – 192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.36 (m, 4H), 7.27 (s, 1H), 7.05 (d, *J* = 7.7 Hz, 2H), 4.85 (s, 1H), 4.47 (s, 2H), 3.89 (s, 3H), 2.52 (s, 3H), 2.48 – 2.27 (m, 2H), 2.19 (s, 2H), 1.06 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 166.9, 164.9, 163.5, 148.0, 144.5, 143.4, 137.2, 134.2, 134.0, 131.7, 131.4, 131.4, 131.0, 130.6, 124.7, 123.1, 119.4, 117.1, 63.7, 60.4, 55.6, 36.7, 33.2, 32.9, 30.8, 14.5. ESI – MS: m/z 548.24 $[M+H]^+$. CHN analysis calcd for $C_{31}H_{29}N_7O_3$: C, 67.99; H, 5.34; N, 17.90 %. Found: C, 67.94; H, 5.29; N, 17.85.

2-Amino-7,7-dimethyl-4-(3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e). Off-white solid. Yield: 92%. m.p.: 188 – 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.70 – 7.61 (m, 5H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.73 (s, 2H), 5.02 (s, 1H), 2.54 (dd, *J* = 4.2, 2.3 Hz, 3H), 2.41 (dd, *J* = 21.4, 9.4 Hz, 2H), 2.18 (q, *J* = 15.8 Hz, 2H), 1.12 – 1.04 (m, 3H), 1.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 167.2, 163.7, 147.9, 144.5, 143.7, 141.2, 137.0, 134.7, 134.5, 132.3, 131.9, 131.1, 130.2, 124.9, 122.9, 117.1, 63.0, 55.5, 36.8, 33.2, 32.9, 30.6, 14.8. ESI – MS: m/z 518.23 $[M+H]^+$. CHN analysis calcd for $C_{30}H_{27}N_7O_2$: C, 69.62; H, 5.26; N, 18.94 %. Found: C, 69.54; H, 5.20; N, 18.79.

2-Amino-7,7-dimethyl-4-(3-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4f). Off-white solid. Yield: 88%. m.p.: 180 – 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.8 Hz, 2H), 8.05 (s, 1H), 7.77 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 4.96 (s, 1H), 4.48 (s, 2H), 2.68 (s, 3H), 2.42 (d, *J* = 33.7 Hz, 2H), 2.21 (d, *J* = 3.3 Hz, 2H), 1.08 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 166.8, 163.5, 152.4, 147.4, 146.1, 144.5, 144.4, 137.2, 134.2, 131.8, 131.1, 130.9, 130.4, 129.8, 124.7, 123.2, 117.2, 63.6, 55.6, 36.8,33.2, 32.9, 30.7, 14.9**.** ESI – MS: m/z 563.21 $[M+H]^+$. CHN analysis calcd for $C_{30}H_{26}N_8O_4$: C, 64.05; H, 4.66; N, 19.92 %. Found: C, 64.00; H, 4.61; N, 19.86.

2-Amino-4-(4-(1-(4-bromophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4g). Off-white solid. Yield: 84%. m.p.: 194 – 196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.71 (s, 5H), 7.50 – 7.34 (m, 4H), 4.89 (s, 1H), 4.44 (s, 2H), 2.57 (s, 3H), 2.40 (dd, *J* = 60.5, 17.5 Hz, 2H), 2.19 (s, 2H), 1.07 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 163.8, 158.0, 143.1, 139.8, 139.1, 136.5, 132.4, 129.9, 129.8, 129.7, 129.5, 129.4, 129.3, 127.8, 126.3, 125.2, 125.0, 123.9, 119.7, 119.2, 118.9, 61.4, 36.9, 29.7, 27.1, 26.5, 20.0, 9.9. ESI – MS: m/z 597.13 $[M+2H]^+$. CHN analysis calcd for $C_{30}H_{26}BrN_7O_2$: C, 60.41; H, 4.39; N, 16.44 %. Found: C, 60.35; H, 4.33; N, 16.39.

2-Amino-4-(3-(5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4h). Off-white solid. Yield: 84%. m.p.: 198 – 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.08 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.36 (q, *J* = 8.5 Hz, 4H), 7.29 (s, 1H), 4.83 (s, 1H), 4.47 (s, 2H), 2.47 (d, *J* = 13.9 Hz, 5H), 2.33 (d, *J* = 6.4 Hz, 2H), 1.96 (d, *J* = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 163.8, 158.1, 143.1, 139.8, 139.6, 138.9, 134.0, 132.5, 130.1, 129.3, 127.7, 126.3, 124.9, 124.0, 119.3, 118.8, 113.3, 61.2, 36.9, 27.1, 26.5, 21.2, 20.0, 9.9. ESI – MS: m/z 504.21 $[M+H]^+$. CHN analysis calcd for $C_{29}H_{25}N_7O_2$: C, 69.17; H, 5.00; N, 19.47 %. Found: C, 69.30; H, 4.94; N, 19.42.

2-Amino-4-(3-(1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4i). Off-white solid. Yield: 89%. m.p.: 202 – 204 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.45 (dd, *J* = 17.0, 8.6 Hz, 4H), 7.28 (d, *J* = 7.4 Hz, 1H), 4.87 (s, 1H), 4.49 (s, 2H), 2.59 (dt, *J* = 11.1, 5.2 Hz, 1H), 2.53 (s, 3H), 2.48 – 2.28 (m, 3H), 1.99 – 1.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.5, 177.6, 163.7, 158.0, 142.9, 139.8, 139.3, 135.4, 135.0, 132.4, 129.8, 129.3, 127.8, 126.4, 126.2, 124.0, 119.1, 118.8, 113.4, 61.5, 36.9, 27.1, 26.5, 20.0, 10.0. ESI – MS: m/z 525.23 $[M+H]^+$. CHN analysis calcd for $C_{28}H_{22}ClN_7O_2$: C, 64.18; H, 4.23; N, 18.71 %. Found: C, 64.12; H, 4.18; N, 18.66.

2-Amino-4-(3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4j). Off-white solid. Yield: 85%. m.p.: 204 – 206 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.74 (dd, *J* = 8.9, 4.8 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 1H), 5.75 (s, 2H), 4.96 (s, 1H), 2.50 (d, *J* = 1.7 Hz, 2H), 2.46 (s, 3H), 2.34 – 2.20 (m, 2H), 1.92 (dt, *J* = 20.0, 10.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.0, 168.5, 163.3, 147.8, 144.5, 143.5, 137.5, 137.4, 134.1, 132.1, 132.0, 131.6, 131.1, 130.8, 124.6, 123.3, 121.4, 121.2, 118.4, 63.7, 41.6, 31.8, 30.7, 24.8, 14.3. ESI – MS: m/z 508.19 $[M+H]^+$. CHN analysis calcd for $C_{28}H_{22}FN_7O_2$: C, 66.26; H, 4.37; N, 19.32 %. Found: C, 66.20; H, 4.31; N, 19.27.

2-Amino-4-(3-(1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4k). Off-white solid. Yield: 84%. m.p.: 194 – 196 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.45 (s, 1H), 7.90 (s, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.82 (s, 1H), 5.76 (s, 2H), 4.97 (s, 1H), 3.88 (s, 3H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.26 (dd, *J* = 16.2, 7.2 Hz, 2H), 1.96 – 1.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 168.7, 164.9, 163.3, 148.0, 144.5, 143.2, 137.4, 134.2, 134.0, 131.6, 131.4, 131.2, 131.0, 124.7, 123.1, 119.5, 118.3, 63.5, 60.4, 41.6, 31.8, 30.7, 24.8, 14.4. ESI – MS: m/z 520.21 $[M+H]^+$. CHN analysis calcd for $C_{29}H_{25}N_7O_3$: C, 67.04; H, 4.85; N, 18.87 %. Found: C, 67.34; H, 4.80; N, 18.82.

2-Amino-4-(3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4l). Off-white solid. Yield: 82%. m.p.: 186 – 188 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.72 – 7.60 (m, 5H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 5.76 (s, 2H), 4.96 (s, 1H), 2.51 (d, *J* = 1.7 Hz, 2H), 2.47 (s, 3H), 2.26 (dd, *J* = 15.7, 7.1 Hz, 2H), 1.97 – 1.89 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 163.7, 158.0, 142.8, 139.8, 135.4, 132.9, 132.8, 132.4, 129.8, 129.3, 127.8, 126.5, 126.4, 124.1, 123.4, 119.7, 118.8, 113.4, 61.5, 36.9, 27.1, 26.4, 20.0, 10.0. ESI – MS: m/z 490.19 $[M+H]^+$. CHN analysis calcd for $C_{28}H_{23}N_7O_2$: C, 68.70; H, 4.74; N, 20.03 %. Found: C, 68.65; H, 4.68; N, 19.97.

2-Amino-4-(3-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4m). Off-white solid. Yield: 80%. m.p.: 182 – 184 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.51 (s, 1H), 8.48 (d, *J* = 6.1 Hz, 2H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.82 (s, 1H), 5.75 (s, 2H), 4.97 (s, 1H), 2.58 (s, 3H), 2.51 (dd, *J* = 6.1, 4.4 Hz, 2H), 2.27 (dd, *J* = 14.9, 7.4 Hz, 2H), 2.00 – 1.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 168.6, 163.4, 152.4, 147.3, 146.1, 144.4, 137.5, 134.2, 131.7, 131.4, 131.1, 130.5, 129.9, 124.6, 124.5, 123.2, 118.5, 63.4, 41.6, 31.8, 30.6, 24.8, 14.8. ESI – MS: m/z 535.18 $[M+H]^+$. CHN analysis calcd for $C_{28}H_{22}N_8O_4$: C, 62.92; H, 4.15; N, 20.96 %. Found: C, 62.88; H, 4.10; N, 20.92.

2-Amino-4-(3-(1-(4-bromophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4n). Off-white solid. Yield: 83%. m.p.: 196 – 198 °C. ^{1}H NMR (400 MHz,

DMSO) δ 8.46 (s, 1H), 7.88 (t, *J* = 7.5 Hz, 4H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.35 – 7.28 (m, 1H), 6.81 (s, 1H), 5.75 (s, 2H), 4.95 (s, 1H), 2.51 (s, 3H), 2.48 (s, 2H), 2.25 (d, *J* = 5.5 Hz, 2H), 1.92 (s, 2H). ^{13}C NMR (126 MHZ, $CDCl_3$) δ 196.5, 163.7, 158.0, 142.8, 139.8, 135.4, 133.0, 132.8, 132.4, 129.8, 129.3, 127.8, 126.5, 126.4, 124.1, 123.4, 119.7, 119.1, 118.8, 113.4, 61.5, 36.9, 27.1, 26.4, 20.0, 10.0. ESI – MS: m/z 569.10 $[M+2H]^+$. CHN analysis calcd for $C_{28}H_{22}BrN_7O_2$: C, 59.16; H, 3.90; N, 17.25 %. Found: C, 59.11; H, 3.85; N, 17.20.

Acknowledgements

All authors thank the Head, Department of Chemistry, Osmania University for providing research facilities.

Supplementary Material

Biological assay procedures, Molecular docking study results and copies of all ^{1}H and ^{13}C NMR spectra of all products are available in the supplementary material.

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By checking the following box, the senior author acknowledges that they and the other authors have read, understood, and complied with the Instructions to Authors (ItA).

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