Microwave-Assisted Rapid Synthesis of Novel 1,5-Benzodiazepine Derivatives as Potent Antimicrobial Agent

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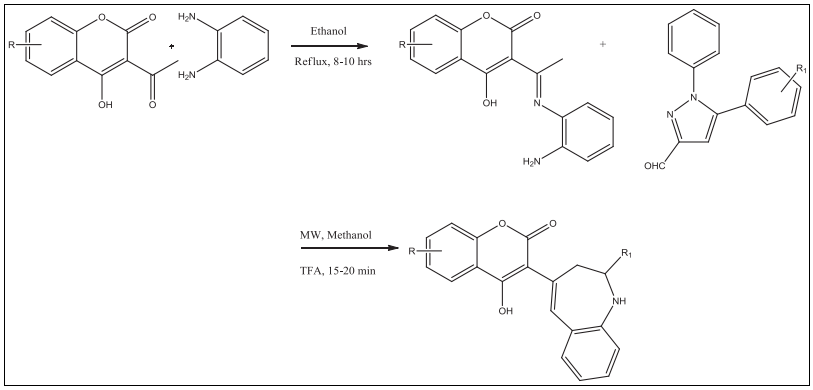

A new series of highly functionalized 1,5-benzodiazepine derivatives **5a–x** have been synthesized from 3-[(1E)-*N*-(2-aminophenyl) ethanimidoyl]-4-hydroxyl-2H-chromen-2-one **3a–c** and pyrazole aldehyde **4a–h** using catalytic amount of triflouro acetic acid under microwave irradiation. The main significant of the present procedure is shorter reaction time, easy work up procedure, and excellent yield with high purity. The structures of all the compounds were established on the basis of their IR, NMR, and mass spectral data and have been screened for their antimicrobial activity and antifungal activity.

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INTRODUCTION

Benzodiazepines have recently received great importance because of their wide range of therapeutic and pharmacological properties. These compounds are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic agents, and anti-inflammatory agents [1,2]. Moreover, benzodiazepine derivatives are commercially used as dyes for acrylic fibers [3]. In the last decade, the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer, viral infection, and cardiovascular disorders [4,5].

In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo-, oxadiazolo-, oxazino-, or furan benzodiazepines [6–9]. Generally, these types of compounds are synthesized by the condensation of *o*-phenylenediamines with α, β-unsaturated carbonyl compounds [10], β-haloketones, or ketones [11]. Because of their versatile applications, various methods for the synthesis of benzodiazepines have been reported in the literature [12–31] (Fig. 1).

Moreover, pyrazole framework containing compounds are well known for its antibacterial, anti HIV, anticancer, anti-inflammatory, analgesic, and hypoglycaemic activities [32]. Pyrazoles are used as insecticids and pesticids because of their herbicidal and fungicidal activity [33]. Recently, pyrazoles containing aryl substituted emerged as p38 Kinase inhibitors, antiparasitic activities [34]. Because of their wide range of biological, industrial, and synthetic applications, the development of mild and efficient protocols continues to be a challenging endeavor in synthetic organic chemistry. These finding prompted us to synthesize pyrazole containing 1,5-benzodiazepines functionalized with 4-hydroxyl coumarin for biological interest. We report here a method for the preparation of highly functionalized 1,5-benzodiazepine derivatives using triflouro acetic acid as catalyst under microwave irradiation.

RESULTS AND DISCUSSION

In the first instance, 3-acetyl 4-hydroxy coumarin **1a–c** was synthesized by reported method [35]. Further, the reaction of 3-acetyl 4-hydroxy coumarin **1a–c** with *o*-phenylene diamine **2** in ethanol for 8–10 h afforded **3a–c** (Scheme 1). Then, the condensation of newly synthesized **3a–c** and **4a–h** in the presence of triflouro acetic acid under microwave irradiation in methanol for 15–20 min afforded **5a–x** (Scheme 2).)

Indeed, the reaction of **4a** with **3a** in different solvents likes methanol, ethanol, isopropanol, Chloroform, THF, ethyl acetate, and DMF was observed using microwave irradiation. Under the optimized conditions, we found that the reaction proceeds well in polar solvents giving slight

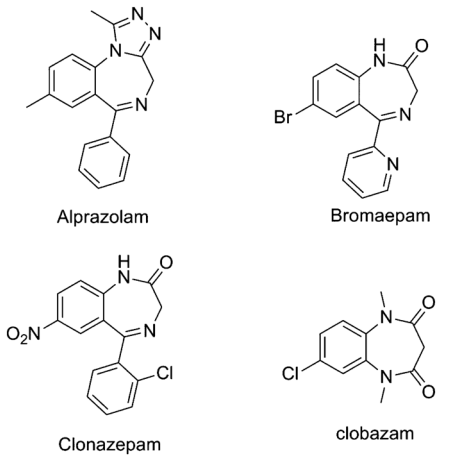


Figure 1. Biologically active benzodiazepine derivatives.

variations in reaction time and that methanol was the best choice for this reaction with high yield. (Tables 1 and 2).

Antimicrobial and antifungal activities of compounds 5a–x. The newly synthesized benzodiazepine compounds **5a–x** have been screened for antimicrobial activity against *Staphylococcus typhi, Staphylococcus pyogenus,* and *Vibrio cholera* and antifungal activity against *Candida albicans* by Broth dialution method [36,37]. Ampicillin, chloramphenicol, nystatin, and greseofulvin were used as standards for comparison of antimicrobial and antifungal activity. The result indicates that some of these compounds were active against all the four organisms. The results of antimicrobial and antifungal activity are cited in Table 3.

Structure–activity relationship. SAR studies enlights that 1,5-benxodiazepines can be optimized for the *S. pyogenus* and also for *S. typhi*. Particularly, compound **5g** can be optimized for the broad spectrum of activity. Herein, $-NO_2$ strong electron donating group induces the potency. Thus, molecules having $-NO_2$ group at 3 position shown more potency. [Molecules (**5l** MIC = 69.8), (**5w** MIC = 62.5)]. Also, compounds having bulky group attached at 5th and 8th position of coumarin ring also favors the potency.

CONCLUSIONS

During the reaction procedure, we have observed that the time taken by **5a** in methanol is less and yield is high when compared with other solvents. In conclusion, a new method developed for novel 1,5-benzothiazepine derivatives, which is rapid and high yielding. The antimicrobial activity of these compounds was evaluated against various bacteria and fungi. Most of the compounds showed a moderate degree of antimicrobial activity. Compound **5g** seems to be most active among the whole data series because it has shown potency to all the four strains, whereas compounds **5h**, **5i**, **5l**, **5o**, **5p**, **5s**, **5w,** and **5**x are moderately active molecules. With this set of analogs, we are now in a position to investigate the multiple biological activities of these compounds.

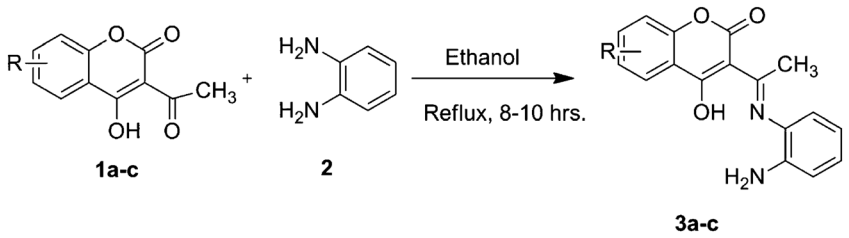
EXPERIMENTAL

All the melting points are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5-mm thickness, and spots were located by iodine and UV. All the reaction was carried out in Q-Pro-M microwave synthesizer. The IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H-NMR was determined in $CDCl_3$/DMSO solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Elemental Vario EL III Carlo Erba 1108 model, and the results are in agreements with the structures assigned.

Synthesis of (E)-3-(1-((2-aminophenyl)imino)ethyl)-4-hydroxy-2*H*-chromen-2-one (3a-c). 3-Acetyl-4-hydroxy coumarin **1a–c** (0.01 mol) and *O*-phenylene diamine **2** (0.01 mol) were dissolved in 30 mL ethanol and refluxed the content for 8–10 h. The reaction was monitored through TLC. Solid separated out a to be filtered and washed with chilled methanol, recrystallize it from mixture of methanol–DMF. Purity of the compounds was checked through TLC using ethyl acetate:hexane (6:4) system as the mobile phase.

General procedure for the synthesis of 3-(2-(1,3(substituted)-dipheyl-*1H*-pyrazol-4-yl)-2,3-dihydro-*1H*-benzo[*b*][1,4]diazepin-4-yl)-4-hydroxy-*2H*-chromen-2-one (5a–x). 3-[(1E)-N-(2-Aminophenyl) ethanimidoyl]-4-hydroxy-2H-chromen-2-one **3a–c** (0.01 mol) and substituted pyrazole aldehydes **4a–h** (0.01 mol) were dissolved in a methanol and subjected to Q-Pro-M microwave synthesizer for appropriate time at 200 W (70°C) with catalytic amount of triflouroacetic acid. During the reaction, the progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate:hexane (3:2) as a mobile phase. Pour the content into crushed ice. The solid separated out

Scheme 1. Synthesis of 3-(2-(1,3(substituted)-dipheyl-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2*H*-chromen-2-one (**5a–x**).



Scheme 2. Synthesis of 3-(2-(1,3(substituted)-dipheyl-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2*H*-chromen-2-one (**5a–x**).

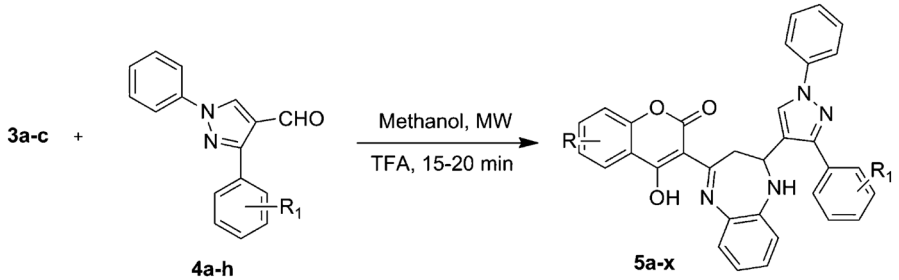


Table 1

Solvent effect on yield.

Entry	Solvent	Time	Yield[a] (%)
5a	MeOH	9	94
5a	EtOH	11	92
5a	IPA	9	89
5a	CH_2Cl_2	12	85
5a	THF	14	89
5a	EA	12	87
5a	DMF	16	82

[a]Isolated yields after purification.

was filtered, washed, dried, and recrystallized it from methanol. Spectral data for selected products **5a–x**.

3-(2-(1,3-Diphenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]dizepin-4-yl)-4-hydroxy-2H-chromen-2-one (5a). Melting point 180–182°C; Yield: 94%; IR (cm^{-1}): 3606, 3425, 3090, 3061, 2988, 2823, 1776, 1606, 1562, 1454, 1429, 1374, 1221, 766, 692, 702. ^{1}H-NMR (DMSO-d_6) δ ppm: 3.28–3.34(d, 2H), 4.45(s, 1H), 5.54–5.59(d, 1H), 6.91–6.93(d, 1H), 7.09–7.15(t, 1H), 7.21–7.27 (m, 5H), 7.31–7.34(t, 2H), 7.46–7.48(d, 2H), 7.52–7.58(t, 3H), 7.64–7.68(t, 1H), 7.76–7.78(d, 2H, J = 8.0 Hz), 8.03(s, 1H), 8.09–8.12(d, 1H), 15.76(s, 1H), MS: m/z = 524.18; Anal. Calcd. for $C_{33}H_{24}N_4O_3$ C, 75.56; H, 4.61; N, 10.68; O, 9.15; Found: C, 75.46; H, 4.56; N, 10.68; O, 9.09(%).

Table 2

Physical data.

	Substitution				Time	Yield[a]
Entry	R_1	R	MF	MP (°C)	(min)	(%)
5a	H	H	$C_{33}H_{24}N_4O_3$	180–182	9	94
5b	4-CH_3	H	$C_{34}H_{26}N_4O_3$	204–206	8	89
5c	4-NO_2	H	$C_{33}H_{23}N_5O_5$	226–228	11	88
5d	2-OH	H	$C_{33}H_{24}N_4O_4$	208–210	7	82
5e	2-OCH_3	H	$C_{34}H_{26}N_4O_4$	196–198	8	89
5f	4-Cl	H	$C_{33}H_{23}ClN_4O_3$	188–190	12	88
5g	3-NO_2	H	$C_{33}H_{23}N_5O_5$	210–212	16	85
5h	4-F	H	$C_{33}H_{23}FN_4O_3$	178–180	6	86
5i	H	8-CH_3	$C_{34}H_{26}N_4O_3$	186–188	8	85
5j	4-CH_3	8-CH_3	$C_{35}H_{28}N_4O_3$	168–170	9	91
5k	4-Cl	8-CH_3	$C_{34}H_{25}ClN_4O_3$	194–196	14	88
5l	4-NO_2	8-CH_3	$C_{34}H_{25}N_5O_5$	206–208	13	86
5m	2-OH	8-CH_3	$C_{34}H_{26}N_4O_4$	178–180	8	88
5n	2-OCH_3	8-CH_3	$C_{35}H_{28}N_4O_4$	166–168	7	92
5o	3-NO_2	8-CH_3	$C_{34}H_{25}N_5O_5$	218–220	18	86
5p	4-F	8-CH_3	$C_{34}H_{25}FN_4O_3$	208–210	9	87
5q	H	5,8-di CH_3	$C_{35}H_{28}N_4O_3$	178–180	8	89
5r	4-CH_3	5,8-di CH_3	$C_{36}H_{30}N_4O_3$	212–214	8	92
5s	4-Cl	5,8-di CH_3	$C_{35}H_{27}ClN_4O_3$	202–204	14	84
5t	4-NO_2	5,8-di CH_3	$C_{35}H_{27}N_5O_5$	182–184	17	89
5u	2-OH	5,8-di CH_3	$C_{35}H_{28}N_4O_4$	176–178	9	87
5v	2-OCH_3	5,8-di CH_3	$C_{36}H_{30}N_4O_4$	218–220	11	92
5w	3-NO_2	5,8-di CH_3	$C_{35}H_{27}N_5O_5$	192–194	18	86
5x	4-F	5,8-di CH_3	$C_{35}H_{27}FN_4O_3$	188–190	8	89

[a]Isolated yields after purification.

Table 3

Antimicrobial and antifungal activities of compounds **5a–x.**

	MIC value (μg/mL)			
Entry	*S.typhi* MTCC-98	*Vi.cholerae* MTCC-3906	*S.pyogenus* MTCC-442	*C.albicans* MTCC-227
5a	500	200	250	**500**
5b	250	250	500	250
5c	250	500	500	250
5d	500	200	200	1000
5e	200	200	200	1000
5f	200	250	200	**500**
5g	**100**	**100**	250	250
5h	**100**	**100**	250	**500**
5i	250	**100**	250	250
5j	200	250	500	250
5k	250	250	500	**500**
5l	**69.8**	250	500	1000
5m	200	250	1000	1000
5n	500	200	250	1000
5o	**100**	**100**	250	**500**
5p	**100**	**100**	500	1000
5q	250	500	250	>1000
5r	250	200	200	**500**
5s	**100**	200	500	**500**
5t	200	250	250	200
5u	200	250	500	200
5v	200	250	500	200
5w	**62.5**	**100**	250	1000
5x	**100**	**100**	200	**500**
Ampicillin	100	100	100	–
Chloramphemicol	50	50	50	–
Nystatin	–	–	–	100
Greseofulvin	–	–	–	500

Bold values indicate that the compounds are active against the standard drugs.

3-(-2,3-Dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4-diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (5b). Melting point 204–206°C; Yield: 89%; IR (cm^{-1}): 3576, 3556, 3525, 3190, 3161, 2978, 2833, 1766, 1676, 1606, 1562, 1492, 1464, 1419, 1354, 1211, 756, 681, 701. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.39(s, 3H), 3.1–3.2(d, 2H), 4.5(s, 1H), 5.55(d, 1H), 6.90–6.93(d, 1H), 7.07–7.11 (t, 1H), 7.21–7.23(d, 2H, *J* = 8.0 Hz), 7.23–7.30(m, 5H), 7.40–7.45(t, 2H), 7.56–7.60(t, 1H), 7.66(d, 2H, *J* = 8.0 Hz), 7.72–7.75(d, 2H, *J* = 8.0 Hz), 8.00(s, 1H), 8.06–8.09 (d, 2H, *J* = 8.0 Hz), 15.70(s, 1H), MS = *m/z* = 538.20; Anal. Calcd. for $C_{34}H_{26}N_4O_3$: C, 75.82; H, 4.87; N, 10.40; O, 8.91; Found: C, 75.81; H, 4.80; N, 10.38; O, 8.81(%).

3-(-2,3-Dihydro-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (5c). Melting point 226–228°C; Yield: 88%; IR (cm^{-1}): 3616, 3435, 3043, 3021, 2978, 2820, 1756, 1616, 1582, 1545, 1444, 1419, 1364, 1211, 756, 691, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 3.25–3.28(d, 2H), 4.47(s, 1H), 5.61(s, 1H), 6.91–6.94(d, 1H), 7.01–7.04(d, 1H), 7.15–7.17(d, 2H, *J* = 8.0 Hz), 7.22–7.31(m, 5H), 7.41–7.45(t, 2H), 7.53–7.58(t, 1H), 7.62–7.64(d, 2H, *J* = 8.0 Hz), 7.71–7.73(d, 2H, *J* = 8.0 Hz), 8.06(s, 1H), 8.12–8.14(d, 2H, *J* = 8.0 Hz), 15.82(s, 1H), MS: *m/z* = 569.57; Anal. Calcd. for $C_{33}H_{23}N_5O_5$: C, 69.59; H, 4.07; N, 12.30; O, 14.05, Found: C, 69.49; H, 4.04; N, 12.21; O, 14.01(%).

3-(-2,3-Dihydro-2-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (5d). Melting point 208–210°C; Yield: 82%; IR (cm^{-1}): 3601, 3523, 3383, 3221, 3115, 3051, 3014, 2945, 2879, 1786, 1674, 1604, 1566, 1483, 1462, 1415, 1346, 1242, 1205, 1159, 1126, 1085, 761,750, 682, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 3.28–3.34(d, 2H), 4.36(s, 1H), 5.33–5.36(s, 1H), 6.91–7.03 (m, 4H), 7.17–7.22(t, 2H), 7.24–7.30(m, 4H), 7.42–7.46 (t, 2H), 7.56–7.61(m, 2H), 7.71–7.73(d, 2H, *J* = 8.0 Hz), 8.00–8.02(d, 1H, *J* = 8.0 Hz), 8.31(s, 1H), 10.00(s, 1H), 15.60 (s, 1H), MS: *m/z* = 540.57; Anal. Calcd. for $C_{33}H_{24}N_4O_4$: C, 73.32; H, 4.48; N, 10.36; O, 11.84, Found: C, 73.24; H, 4.45; N, 10.30; O, 11.79(%).

3-(-2,3-Dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]dizepin-4-yl)-4-hydroxy-2H-chromen-2-one (5e). Melting point 196–198°C; Yield: 89%; IR (cm^{-1}): 3668, 3468, 3271, 3097, 3012, 2978, 2901, 1766, 1697, 1604, 1467, 1423, 1340, 1290, 1236, 1201, 1120, 1022, 765, 688, 708. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.85–3.00(q, 2H), 3.83(s, 3H), 4.49–4.52(s, 1H), 5.23–5.26 (d, 1H), 6.59–6.61(d, 1H, *J* = 8.0 *Hz*), 6.98–7.01(d, 2H), 7.02–7.10(m, 2H), 7.11–7.20(m, 4H), 7.26–7.31(m, 3H), 7.54–7.59 (t, 2H), 7.66–7.68(d, 2H, *J* = 8.0 Hz), 7.85(s, 1H), 15.59(s, 1H), MS: *m/z* = 554.59; Anal. Calcd. for $C_{34}H_{26}N_4O_4$: C, 73.63; H, 4.73; N, 10.10; O, 11.54 Found: C, 73.43; H, 4.59; N, 10.03; O, 11.43(%).

3-(-2-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (5f). Melting point 188–190°C; Yield: 88%; IR (cm^{-1}): 3568, 3448, 3071, 3037, 2988, 2891, 1746, 1687, 1624, 1453, 1440, 1236, 1286, 1201, 1120, 755, 688, 702. ^{1}H-NMR (DMSO-d_6) δ ppm: 3.17–3.19(d, 2H), 4.49(s, 1H), 5.47(s, 1H), 6.82–6.85(t, 1H), 7.01–7.03(d, 1H), 7.25–7.27(d, 2H, *J* = 8.0 Hz), 7.20–7.27(m, 5H), 7.45–7.49(t, 2H), 7.51–7.55(t, 1H), 7.64–7.66(d, 2H, *J* = 8.0 Hz), 7.78–7.82(d, 2H, *J* = 8.0 Hz), 8.19(s, 1H), 8.16–8.18(d, 1H, *J* = 8.0 Hz), 15.73 (s, 1H), MS: *m/z* = 559(M^+), 562(M^{+2}); Anal. Calcd. for $C_{33}H_{23}ClN_4O_3$: C, 70.90; H, 4.15; Cl, 6.34; N, 10.02; O, 8.59 Found: C, 70.81; H, 4.07; Cl,6.30; N, 10.05; O, 8.46(%).

3-(-2,3-Dihydro-2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (5g). Melting point 210–212°C; Yield: 85%; IR (cm^{-1}): 3623, 3323, 3115, 3041, 2935, 2869, 1776, 1675, 1634, 1560, 1482, 1425, 1326, 1232, 1215, 1169, 1136, 1075, 771, 760, 672, 719. ^{1}H-NMR (DMSO-d_6) δ ppm: 3.13–3.16(d, 2H), 4.52(s, 1H), 5.56 (s, 1H), 6.92–6.95(d, 1H), 7.17–7.20(t, 1H), 7.21–7.23(s, 1H), 7.25–7.27(d, 1H, *J* = 8.0 Hz), 7.30–7.33(d, 2H), 7.36–7.45 (m, 5H), 7.49–7.45(t, 2H), 7.56–7.60(t, 1H), 7.66–7.68(d, 2H, *J* = 8.0 Hz), 8.03(s, 1H), 8.06–8.09(d, 1H, *J* = 8.0 Hz), 15.92 (s, 1H), MS: *m/z* = 569.57; Anal. Calcd. for $C_{33}H_{23}N_5O_5$: C, 69.59; H, 4.07; N, 12.30; O, 14.05 Found: C, 69.54; H, 4.06; N, 12.21; O, 14.02(%).

3-(-2-(3-(4-Flourophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihylro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (5h). Melting point 178–180°C; Yield: 86%; IR (cm^{-1}): 3523, 3343, 3015, 3011, 2945, 2879, 1786, 1685, 1644, 1472, 1435, 1282, 1245, 1210, 1136, 761, 750, 692, 709. ^{1}H-NMR (DMSO-d_6) δ ppm 3.21–3.25(d, 2H), 4.45(s, 1H), 5.45(s, 1H), 6.83–6.87(t, 1H), 7.10–7.13(d, 1H), 7.21–7.25(d, 2H, *J* = 8.0 Hz), 7.28–7.35(m, 5H), 7.45–7.49(t, 2H), 7.55–7.59(t, 1H), 7.66–7.68(d, 2H, *J* = 8.0 Hz), 7.76–7.78(d, 2H, *J* = 8.0 Hz), 8.18(s, 1H), 8.21–8.24(d, 1H, *J* = 8.0 Hz), 15.72(s, 1H), MS:

m/z = 542, 544(M^{+2}); Anal. Calcd. for $C_{33}H_{23}FN_4O_3$: C, 73.05; H, 4.27; F, 3.50; N, 10.33; O, 8.85 Found: C, 73.00; H, 4.21; F, 3.42; N, 10.23; O, 8.75(%).

3-(-2,3-Dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5i). Melting point 186–188°C; Yield: 85%; IR (cm^{-1}): 3616, 3445, 3110, 3051, 2978, 2833, 1786, 1696, 1602, 1464, 1439, 1364, 1291, 1236, 1211, 1146, 765, 692, 719. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.59(s, 3H), 3.17–3.22(d, 2H), 4.49(s, 1H), 5.50(s, 1H), 6.92–6.95(t, 1H), 7.07–7.11 (d, 1H), 7.23–7.25(d, 2H, *J* = 8.0 Hz), 7.33–7.40(m, 5H), 7.40–7.45(t, 2H), 7.66–7.68(d, 2H), 7.76(d, 2H, *J* = 8.0 Hz), 8.02(s, 1H), 8.06–8.09(d, 2H), 15.89(s, 1H), MS: *m/z* = 538.60; Anal. Calcd. for $C_{34}H_{26}N_4O_3$: C,75.82; H, 4.87; N, 10.40; O, 8.91 Found: C, 72.83; H, 4.81;O, 8.89(%).

3-(-2,3-Dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-mehyl-2H-chromen-2-one (5j). Melting point 168–170°C; Yield: 91%; IR (cm^{-1}): 3609, 3435, 3190, 3051, 2978, 2843, 1777, 1616, 1572, 1439, 1384, 1211, 1212, 1146, 756, 681, 701. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.29(s, 3H), 2.49(s, 3H), 3.21–3.26(d, 2H), 4.47 (s, 1H), 5.58(s, 1H), 6.92–6.95(t, 1H), 7.18–7.20(d, 1H), 7.22–7.24(d, 2H, *J* = 8.0 Hz), 7.39–7.45(m, 5H), 7.55–7.59 (t, 2H), 7.69–7.71(d, 2H, *J* = 8.0 Hz), 7.81–7.83(d, 2H, *J* = 8.0 Hz), 8.27(s, 1H), 8.16–8.89(d, 1H, *J* = 8.0 Hz), 15.79 (s, 1H), MS: *m/z:* 552.62; Anal. Calcd. for $C_{35}H_{28}N_4O_3$: C, 76.07; H, 5.11; N, 10.14; O, 8.69 Found: C, 76.03; H, 5.01; N, 10.07; O, 8.60(%).

3-(-2-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5k). Melting point 194–196°C; Yield: 88%; IR (cm^{-1}): 3599, 3445, 3090, 3052, 2988, 2853, 1767, 1606, 1562, 1449, 1374, 1221, 1201, 1126, 776, 689, 703. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.39 (s, 3H), 3.18–3.22(d, 2H), 4.39(s, 1H), 5.59(s, 1H), 6.91–6.94(d, 1H), 7.04–7.10(d, 1H), 7.21–7.23(d, 2H, *J* = 8.0 Hz), 7.23–7.30(m, 5H), 7.40–7.45(t, 2H), 7.66(d, 2H, *J* = 8.0 Hz), 7.72–7.75(d, 2H, *J* = 8.0 Hz), 8.21 (s, 1H), 8.02–8.04(d, 1H, *J* = 8.0 Hz), 15.77(s, 1H), MS: *m/z* = 573, 575(M^{+2}); Anal. Calcd. for $C_{34}H_{25}ClN_4O_3$: C, 71.26; H, 4.40; Cl, 6.19; N, 9.78; O, 8.38 Found: C, 71.23; H, 4.31; Cl, 6.77; O, 8.31(%).

3-(-2,3-Dihydro-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5l). Melting point 206–208°C; Yield: 86%; IR (cm^{-1}): 3589, 3435, 3190, 3062, 2998, 2863, 1787, 1616, 1542, 1560, 1469, 1382, 1221, 1212, 1146, 766, 692, 701. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.41(s, 3H), 3.21–3.24(d, 2H), 4.45 (s, 1H), 5.52(s, 1H), 6.91–6.93(d, 1H), 7.01–7.05(t, 1H), 7.20–7.22(d, 2H, *J* = 8.0 Hz), 7.29–7.38(m, 5H), 7.41–7.45 (t, 2H), 7.68–7.70(d, 2H, *J* = 8.0 Hz), 7.82–7.84(d, 2H, *J* = 8.0 Hz), 8.10(s, 1H), 8.12–8.14(d, 1H, *J* = 8.0 Hz), 15.61 (s, 1H), MS: *m/z* = 583.59; Anal. Calcd. for $C_{34}H_{25}N_5O_5$: C, 69.97; H, 4.32; N, 12.00; O, 13.71 Found: C, 69.83; H, 4.31; N, 11.77; O, 13.69(%).

3-(-2,3-Dihydro-2-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5m). Melting point 178–180°C; Yield: 88%; IR (cm^{-1}): 3609, 3445, 3090, 3072, 2998, 2873, 1777, 1626, 1532, 1489, 1372, 1320, 1281, 1219, 1116, 766, 692, 719. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.33(s, 3H), 3.28–3.34(d, 2H), 4.36(s, 1H), 5.33–5.36(s, 1H), 6.91–7.03(m, 4H), 7.17–7.22 (t, 2H), 7.24–7.30(m, 4H), 7.42–7.46(t, 2H), 7.56–7.61 (m, 2H), 7.71–7.73(d, 2H, *J* = 8.0 Hz), 8.31(s, 1H), 10.00 (s, 1H), 15.60(s, 1H), MS: *m/z* = 554.59; Anal. Calcd. for $C_{34}H_{26}0_4N_4$: C, 73.63; H, 4.73; N, 10.10; O, 11.54 Found: C, 73.53; H, 4.61; N, 9.77; O, 11.41(%).

3-(-2,3-Dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]dizepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5n). Melting point 166–168°C; Yield: 92%; IR (cm^{-1}): 3609, 3445, 3090, 3072, 2998, 2873, 1777, 1626, 1532, 1489, 1372, 1320, 1281, 1219, 1116, 766, 692, 719. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.45(s, 3H), 2.85–3.00(q, 2H), 3.80(s, 3H), 4.41(s, 1H), 5.25–5.28(d, 1H), 6.58(d, 1H, *J* = 8.0 *Hz*), 6.98–7.03(d, 2H), 7.17–7.24(m, 2H), 7.27–7.36 (m, 4H), 7.38–7.42(m, 3H), 7.48–7.53(t, 2H), 7.74–7.76(d, 2H, *J* = 8.0 Hz), 7.93(s, 1H), 8.13–8.16(d, 1H), 15.69(s, 1H), MS: *m/z* = 568.62; Anal. Calcd. for $C_{35}H_{28}N_4O_4$: C, 73.93; H, 4.96; N, 9.85; O, 11.25 Found: C, 73.83; H, 4.81; N, 9.67; O, 11.15(%).

3-(-2,3-Dihydro-2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5o). Melting point 218–220°C; Yield: 86%; IR (cm^{-1}): 3619, 3415, 3091, 3071, 2978, 2872, 1787, 1616, 1531, 1561, 1488, 1371, 1321, 1271, 1209, 1106, 776, 691, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.70(s, 3H), 3.31–3.34 (d, 2H), 4.45(s, 1H), 5.65(s, 1H), 6.92–6.95(d, 1H), 7.09–7.14 (t, 1H), 7.25(s, 1H), 7.29–7.31(d, 1H, *J* = 8.0 Hz), 7.39–7.41 (d, 2H), 7.44–7.50(m, 5H), 7.54–7.58(t, 2H), 7.61–7.64 (s, 2H), 8.05(s, 1H), 8.06–8.09(d, 1H, *J* = 8.0 Hz), 15.61 (s, 1H), MS: *m/z* = 583.59; Anal. Calcd. for $C_{34}H_{25}N_5O_5$: C, 69.97; H, 4.32; N, 12.00; O, 13.71 Found: C, 69.91; H, 4.31; N, 10.77; O, 13.69(%).

3-(-2-(3-(4-Flourophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihylro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one (5p). Melting point 208–210°C; Yield: 87%; IR (cm^{-1}): 3589, 3455, 3098, 3082, 2988, 2883, 1778, 1636, 1522, 1479, 1382, 1321, 1282, 1209, 1110, 767, 691, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.59(s, 3H), 3.19–3.23 (d, 2H), 4.51(s, 1H), 5.59(s, 1H), 6.79–6.82(t, 1H), 7.10–7.13(d, 2H), 7.26–7.34(m, 5H), 7.45–7.49(t, 2H), 7.70–7.72 (d, 2H, *J* = 8.0 Hz), 7.80–7.82(d, 2H, *J* = 8.0 Hz), 8.01(s, 1H), 8.26–8.28(d, 1H, *J* = 8.0 Hz), 15.71(s, 1H), MS: *m/z* = 556, 558 (M^{+2}); Anal. Calcd. for $C_{34}H_{25}FN_4O_3$: C, 73.37; H, 4.53; F, 3.41; N, 10.07; O, 8.62 Found: C, 73.31; H, 4.51; F, 3.37; O, 10.01(%).

3-(-2,3-Dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5q). Melting point 178–180°C; Yield: 89%; IR (cm^{-1}): 3601, 3435, 3080, 3062, 2988, 2883, 1776, 1636, 1542, 1479, 1382, 1321, 1271, 1219, 1117, 767, 691, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.31(s, 6H), 3.19–3.22(d, 2H), 4.54(s, 1H), 5.51(s, 1H), 6.92–6.95 (d, 1H), 7.17–7.20(t, 1H), 7.21–7.23(d, 2H, *J* = 8.0 Hz), 7.23–7.30(m, 5H), 7.40–7.45(t, 2H), 7.56–7.60(t, 3H), 7.66 (d, 2H, *J* = 8.0 Hz), 8.09(s, 1H), 15.21(s, 1H), MS: *m/z* = 552.62; Anal. Calcd. for $C_{35}H_{28}N_4O_3$: C, 76.07; H, 5.11; N, 10.14; O, 8.69 Found: C, 76.05; H, 5.01; N, 10.07; O, 8.58(%).

3-(-2,3-Dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5r). Melting point 212–214°C; Yield: 92%; IR (cm^{-1}): 3619, 3455, 3091, 3082, 2997, 2871, 1767, 1616, 1542, 1499, 1371, 1310, 1271, 1218, 1106, 776, 682, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.19 (s, 6H), 2.95(s, 3H), 3.25–3.26(d, 2H), 4.47(s, 1H), 5.67(s, 1H), 6.86–6.91(t, 1H), 7.08–7.12(d, 1H), 7.23–7.25(d, 2H, *J* = 8.0 Hz), 7.27–7.33(m, 5H), 7.41–7.46 (t, 2H), 7.70–7.72(d, 2H, *J* = 8.0 Hz), 7.79–7.81(d, 2H, *J* = 8.0 Hz), 8.19(s, 1H), 15.60(s, 1H), MS: *m/z* = 566.65; Anal. Calcd.

for $C_{36}H_{30}N_4O_3$: C,76.31; H, 5.34; N, 9.89; O, 8.47 Found: C, 76.23; H, 5.31; N, 9.77; O, 8.44(%).

3-(-2-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5s). Melting point 202–204°C; Yield: 84%; IR (cm^{-1}): 3639, 3455, 3099, 3071, 2988, 2883, 1778, 1616, 1542, 1499, 1382, 1321, 1271, 1229, 1106, 776, 682, 729. ^{1}H-NMR (DMSO-d_6) δ ppm : 2.29 (s, 6H), 3.20–3.23(d, 2H), 4.40(s, 1H), 5.77(s, 1H), 6.87–6.91(t, 1H), 7.18–7.21(d, 1H), 7.33–7.35(d, 2H, *J* = 8.0 Hz), 7.41–7.49(m, 5H), 7.51–7.56 (t, 2H), 7.75–7.77(d, 2H, *J* = 8.0 Hz), 7.91–7.93(d, 2H, *J* = 8.0 Hz), 8.29(s, 1H), 15.94(s, 1H), MS: *m/z* = 587, 589(M^{+2}); Anal. Calcd. for $C_{35}H_{27}ClN_4O_3$: C, 71.61; H, 4.64; Cl, 6.04; N, 9.54; O, 8.18 Found: C, 71.53; H, 4.51; Cl, 6.01; N, 9.51; O, 8.17(%).

3-(-2,3-Dihydro-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5t). Melting point 182–184°C; Yield: 89%; IR (cm^{-1}): 602, 3435, 3190, 3072, 2988, 2863, 1776, 1636, 1531, 1570, 1479, 1378, 1320, 1209, 769, 719. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.71(s, 6H), 3.12–3.15(d, 2H), 4.41(s, 1H), 5.45(s, 1H), 6.81–6.84(t, 1H), 7.09–7.11(d, 1H), 7.22–7.24(d, 2H, *J* = 8.0 Hz), 7.29–7.35(m, 5H), 7.57–7.60 (t, 2H), 7.60–7.62(d, 2H, *J* = 8.0 Hz), 7.73–7.75(d, 2H, *J* = 8.0 Hz), 8.31(s, 1H), 15.48(s, 1H), MS: *m/z* = 597.62; Anal. Calcd. for $C_{35}H_{27}N_5O_5$: C, 70.34; H, 4.55; N, 11.72; O,1 3.39 Found: C, 70.33; H, 4.51; N, 11.67; O, 13.26(%).

3-(-2,3-Dihydro-2-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5u). Melting point 176–178°C; Yield: 87%; IR (cm^{-1}): 3612, 3455, 3191, 3032, 2998, 2861, 1786, 1646, 1541, 1479, 1378, 1321, 1219, 759, 709. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.63(s, 6H), 3.38–3.41(d, 2H), 4.56(s, 1H), 5.23(s, 1H), 6.92–7.02 (m, 4H), 7.27–7.32 (t, 1H), 7.34–7.39(m, 4H), 7.52–7.56(t, 2H), 7.66 -7.76(m, 2H), 7.81–7.83(d, 2H, *J* = 8.0 Hz), 8.41(s, 1H), 10.50(s, 1H), 15.69(s, 1H), MS: *m/z* = 568.62; Anal. Calcd. for $C_{35}H_{28}N_4O_4$: C,73.93; H, 4.96; N, 9.85; O, 11.25 Found: C, 73.83; H, 9.81; N, 9.77; O, 11.24(%).

3-(-2,3-Dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]dizepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5v). Melting point 218–220°C; Yield: 92%; IR (cm^{-1}): 3612, 3455, 3110, 3012, 2981, 2861, 1778, 1632, 1533, 1478, 1379, 1320, 1208, 768, 718. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.12(s, 6H), 2.39(s, 3H), 3.12–3.162(d, 2H), 4.59(s, 1H), 5.35 (s, 1H), 6.59–6.61(d, 1H, *J* = 8.0 *Hz*), 6.91–9.95(d, 2H), 7.06–7.15(m, 2H), 7.17–7.26(m, 4H), 7.36–7.41(m, 3H), 7.49–7.53(t, 2H), 7.64–7.66(d, 2H, *J* = 8.0 Hz), 7.83(s, 1H), 8.03–8.05(d, 1H), 16.21(s, 1H), MS: *m/z* = 582.65; Anal. Calcd. for $C_{36}H_{30}N_4O_4$: C, 74.21; H, 5.19; N, 9.62; O, 10.98 Found: C, 74.13; H, 5.11; N, 9.57; O, 10.91(%).

3-(-2,3-Dihydro-2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5w). Melting point 192–194°C; Yield: 86%; IR (cm^{-1}): 3582, 3445, 3120, 3071, 2998, 2863, 1776, 1636, 1531, 1570, 1479, 1378, 1320, 1209, 769, 719. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.70(s, 6H), 3.13–3.24(d, 2H), 4.35 (s, 1H), 5.55(s, 1H), 6.82–6.85(d, 1H), 7.01–7.04(t, 1H), 7.15 (s, 1H), 7.19–7.21(d, 1H, *J* = 8.0 Hz), 7.29–7.31(d, 2H), 7.54–7.60(m, 5H), 7.64–7.68(t, 2H), 7.71–7.64(d, 2H), 8.05 (s, 1H), 15.61(s, 1H), MS: *m/z* = 597.62; Anal. Calcd. for $C_{35}H_{27}N_5O_5$: C, 70.34; H, 4.55; N, 11.72; O, 13.39 Found: C, 70.23; H, 4.51; N, 11.67; O, 13.31(%).

3-(-2-(3-(4-Flourophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihylro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one (5x). Melting point 188–190°C; Yield: 89%; IR (cm^{-1}): 3612, 3445, 3191, 3082, 2998, 2861, 1786, 1626, 1521, 1478, 1388, 1321, 1201, 768, 718. ^{1}H-NMR (DMSO-d_6) δ ppm: 2.79(s, 6H), 3.15–3.17(d, 2H), 4.49(s, 1H), 5.55(s, 1H), 6.82–6.86(t, 1H), 7.10–7.13(d, 1H), 7.42–7.44(d, 2H, *J* = 8.0 Hz), 7.49–7.59(m, 5H), 7.67–7.73(t, 2H), 7.80–7.82(d, 2H, *J* = 8.0 Hz), 7.93–7.95(d, 2H, *J* = 8.0 Hz), 8.36(s, 1H), 15.58 (s, 1H), MS: *m/z* = 570, 572(M^{+2}); Anal. Calcd. for $C_{35}H_{27}FN_4O_3$: C, 73.67; H, 4.77; F, 3.33; N, 9.82; O, 8.41 Found: C, 73.65; H, 4.59; F, 3.27; N, 9.79; O, 8.32(%).

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