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Microwave-assisted solvent-free synthesis of 3-[(4-substituted piperazin-1-yl)alkyl] imidazo[2,1-*b*][1,3]benzothiazol-2(3*H*)-ones as serotonin$_3$ (5-HT$_3$) receptor antagonists

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A series of novel 3-[(4-substituted piperazin-1-yl)alkyl]imidazo[2,1-*b*][1,3]benzothiazol-2(3*H*)-ones were prepared by microwave irradiation using alumina as solid support and also by a conventional method. The compounds were characterized by spectral data and the purity was ascertained by microanalysis. The synthesized compounds were evaluated for 5-hydroxytryptamine$_3$ antagonisms in a longitudinal muscle-myenteric plexus preparation from guinea pig ileum against the 5-hydroxytryptamine$_3$ agonist, 2-methyl-5-hydroxytryptamine. Among the test compounds, 3-[2-(4-methylpiperazin-1-yl)ethyl]imidazo[2,1-*b*][1,3]benzothiazol-2(3*H*)-one (**3b**) showed most favorable 5-hydroxytryptamine$_3$ antagonism (pA$_2$ 6.7) in the isolated guinea pig ileum.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter involved in various pharmacological effects in several peripheral and central nervous systems (CNS) (Boess and Martin 1994). Fifteen 5-HT receptor subtypes belonging to 7 major classes (5-HT$_1$ 5HT$_7$) have been identified so far (Hoger and Martin 1997). Recently, the 5-HT$_3$ receptor subtype has gained much attention because of the clinical use of 5-HT$_3$ antagonists in the treatment of cancer chemotherapy-induced nausea and vomiting (Karim et al. 1996) and also in postoperative nausea and vomiting (PONV) (Negus and Markocic 2003; Gardner and Perren 1998). Moreover, a number of preclinical studies suggest that 5-HT$_3$ receptor antagonists can be used in the treatment of various CNS disorders like anxiety and cognitive dysfunction (Jones and Blackburn 2002).

In recent years, Microwave Assisted Organic Synthesis (MAOS) (Santagada et al. 2002) has received considerable attention among synthetic/medicinal chemists due to short reaction time, cleaner reaction with an easier work-up and better yields besides being eco-friendly. An improved fea-

Scheme

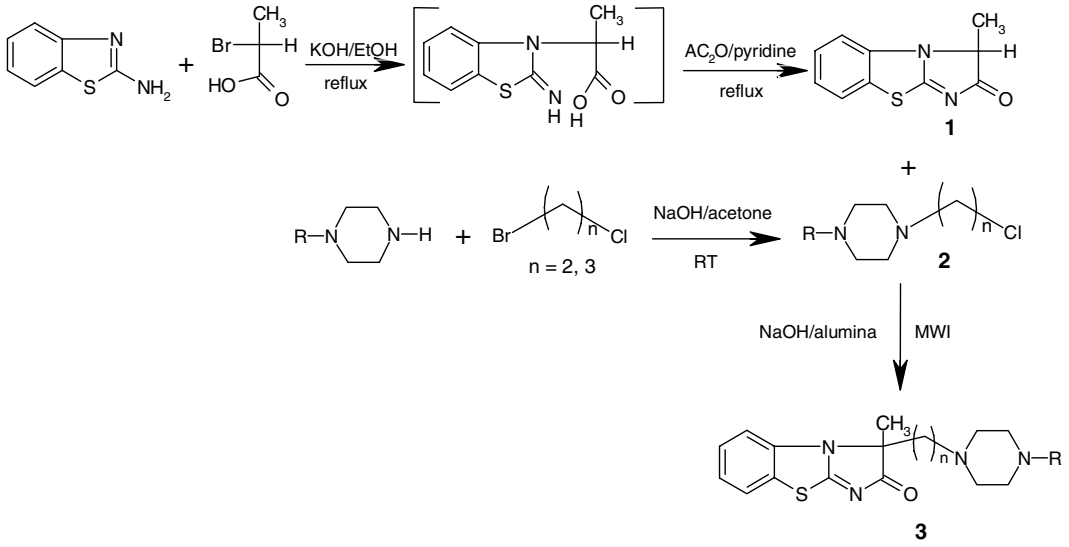
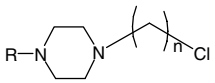


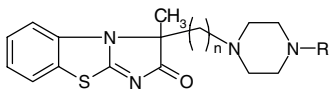
Table 1: Physical data for 1-(chloroalkyl)-4-substituted piperazines



Compd.	R	n	Yield (%)	M.p. (°C)	Mol. formula[a]	Mol. weight[b]
2a	−H	2	86	291–93	$C_6H_{13}ClN_2 \cdot HCl$	184
2b	$-CH_3$	2	78	227–30	$C_7H_{15}ClN_2 \cdot 2\ HCl$	234
2c	$-C_2H_5$	2	82	207–10	$C_8H_{17}ClN_2 \cdot 2\ HCl$	248
2d	$-C_6H_5$	2	76	244–47	$C_{12}H_{17}ClN_2 \cdot 2\ HCl$	260
2e	$-CH_2C_6H_5$	2	79	231–33	$C_{13}H_{19}ClN_2 \cdot HCl$	274
2f	*o*-$OCH_3-C_6H_4$	2	85	>300	$C_{13}H_{19}ClN_2O \cdot HCl$	290
2g	*m*-$OCH_3-C_6H_4$	2	81	236–39	$C_{13}H_{19}ClN_2O \cdot 2\ HCl$	326
2h	*p*-$OCH_3-C_6H_4$	2	79	229–32	$C_{13}H_{19}ClN_2O \cdot 2\ HCl$	326
2i	2-pyridyl	2	83	255–57	$C_{11}H_{16}ClN_3 \cdot 2\ HCl$	297
2j	*p*-Cl−C_6H_4	2	77	254–56	$C_{12}H_{16}Cl_2N_2 \cdot 2\ HCl$	331
2k	*p*-$NO_2-C_6H_4$	2	89	>300	$C_{12}H_{16}Cl_2N_3O_2 \cdot HCl$	305
2l	*m*-$CF_3-C_6H_4$	2	79	224–27	$C_{13}H_{16}ClF_3N_2 \cdot HCl$	328
2m	−H	3	82	>300	$C_7H_{15}ClN_2 \cdot HCl$	198
2n	$-CH_3$	3	80	242–45	$C_8H_{17}ClN_2 \cdot 2\ HCl$	248
2o	$-C_2H_5$	3	78	221–23	$C_9H_{19}ClN_2 \cdot 2\ HCl$	262
2p	$-C_6H_5$	3	75	263–65	$C_{13}H_{19}ClN_2 \cdot HCl$	274
2q	$-CH_2C_6H_5$	3	83	245–47	$C_{14}H_{21}ClN_2 \cdot HCl$	288
2r	*o*-$OCH_3-C_6H_4$	3	79	>300	$C_{14}H_{21}ClN_2O \cdot HCl$	304
2s	*m*-$OCH_3-C_6H_4$	3	81	247–50	$C_{14}H_{21}ClN_2O \cdot 2\ HCl$	340
2t	*p*-$OCH_3-C_6H_4$	3	83	252–55	$C_{14}H_{21}ClN_2O \cdot 2\ HCl$	340
2u	2-pyridyl	3	80	277–80	$C_{12}H_{18}ClN_3 \cdot 2\ HCl$	311
2v	*p*-Cl−C_6H_4	3	75	271–73	$C_{13}H_{18}Cl_2N_2 \cdot 2\ HCl$	345
2w	*p*-$NO_2-C_6H_4$	3	84	>300	$C_{13}H_{18}ClN_3O_2 \cdot HCl$	319
2x	*m*-$CF_3-C_6H_4$	3	76	242–44	$C_{14}H_{18}ClF_3N_2 \cdot HCl$	342

[a] Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (0.4%).
[b] Molecular weight was determined by mass spectral analysis.

Table 2: Physical and pharmacological data for 3-[2-(4-substituted piperazin-1-yl)alkyl]imidazo[2,1-b][1,3]benzothiazol-2(3*H*)-ones



Compd.	R	n	Yield (%)	M.p. (°C) (Recryst. solvent[a])	Mol. formula[b]	Mol. weight[c]	Antagonism to 2-Me-5-HT pA_2[d]
3a	−H	2	65	254–57 (E)	$C_{16}H_{20}N_4OS$	316	6.1
3b	$-CH_3$	2	76	176–78 (E-A)	$C_{17}H_{22}N_4OS$	330	6.7
3c	$-C_2H_5$	2	69	155–57 (E-A)	$C_{18}H_{24}N_4OS$	344	6.4
3d	$-C_6H_5$	2	67	193–96 (A)	$C_{22}H_{24}N_4OS$	392	4.0
3e	$-CH_2C_6H_5$	2	71	184–85 (A)	$C_{23}H_{26}N_4OS$	406	<3.5
3f	*o*-OCH_3-C_6H_4	2	74	249–52 (M-A)	$C_{23}H_{26}N_4O_2S$	422	3.7
3g	*m*-OCH_3-C_6H_4	2	67	181–83 (A)	$C_{23}H_{26}N_4O_2S$	422	5.9
3h	*p*-OCH_3-C_6H_4	2	69	175–77 (M-A)	$C_{23}H_{26}N_4O_2S$	422	3.5
3i	2-pyridyl	2	66	203–06 (A)	$C_{21}H_{23}N_5OS$	393	<3.5
3j	*p*-Cl-C_6H_4	2	70	195–97 (A)	$C_{22}H_{23}ClN_4OS$	426	<3.5
3k	*p*-NO_2-C_6H_4	2	77	264–66 (C)	$C_{22}H_{23}N_5O_3S$	437	<3.5
3l	m-$CF_3-C_6H_4$	2	69	169–72 (A)	$C_{23}H_{23}F_3N_4OS$	460	3.5
3m	−H	3	70	269–71 (E)	$C_{17}H_{22}N_4OS$	330	5.0
3n	$-CH_3$	3	72	191–94 (E-A)	$C_{18}H_{24}N_4OS$	344	5.5
3o	$-C_2H_5$	3	69	172–75 (A)	$C_{19}H_{26}N_4OS$	358	5.2
3p	$-C_6H_5$	3	71	209–11 (A)	$C_{23}H_{26}N_4OS$	406	<3.5
3q	$-CH_2C_6H_5$	3	73	199–202 (A)	$C_{24}H_{28}N_4OS$	420	<3.5
3r	*o*-$OCH_3-C_6H_4$	3	69	266–67 (M-A)	$C_{24}H_{28}N_4O_2S$	436	<3.5
3s	*m*-$OCH_3-C_6H_4$	3	74	200–02 (A)	$C_{24}H_{28}N_4O_2S$	436	4.5
3t	*p*-$OCH_3-C_6H_4$	3	68	195–97 (M-A)	$C_{24}H_{28}N_4O_2S$	436	<3.5
3u	2-pyridyl	3	65	219–22 (A)	$C_{22}H_{25}N_5OS$	407	<3.5
3v	*p*-Cl−C_6H_4	3	68	213–15 (A)	$C_{23}H_{25}ClN_4OS$	440	<3.5
3w	*p*-$NO_2-C_6H_4$	3	75	277–80 (C)	$C_{23}H_{25}N_5O_3S$	451	<3.5
3x	*m*-$CF_3-C_6H_4$	3	66	183–85 (A-C)	$C_{24}H_{25}F_3N_4OS$	474	<3.5
Ondansetron							6.9

[a] Abbreviations for the solvents used are as follows: A = acetone, C = chloroform, E = ethanol, M = methanol.
[b] Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%).
[c] Molecular weight was determined by mass spectral analysis.
[d] Values are the means from three separate experiments. SE was less than 10% of the mean.

ture of MAOS is the possibility of carrying out organic reactions in the presence of inorganic solid support, which eliminates the exposure to toxic solvents/vapours as well as the use of solvents drastically, and ultimately avoiding the risk of high pressure and explosion due to solvents (Galema 1997). In view of the various therapeutic implications of 5-HT_3 receptor antagonists and in continuation of our interest in MAOS (Mahesh and Venkatesha Perumal 2004), herein, we wish to report a simple, convenient and rapid microwave-assisted solvent-free synthesis of 3-[(4-substituted piperazin-1-yl)alkyl]imidazo[2,1-*b*][1,3]benzothiazol-2(3*H*)-ones. The synthetic pathway is represented in the Scheme. All the new chemical entities were evaluated for 5-HT_3 antagonism in the longitudinal muscle-myenteric plexus (LMMP) preparation of guinea pig ileum against the 5-HT_3 agonist, 2-methyl-5-HT.

2. Investigations, results and discussion

The title compounds, 3-[(4-substituted piperazin-1-yl)alkyl]imidazo[2,1-*b*][1,3]benzothiazol-2(3*H*)-ones (**3**) were prepared by the reaction of 2-oxo-3-methyl-2,3-dihydroimidazo[2,1-*b*]benzothiazole (**1**) and the appropriate 1-(chloroalkyl)piperazine (**2**), using neutral alumina as solid support in a microwave environment for about 5 min at 900 W. In conventional heating, the reactants were dissolved in ethanol and refluxed in an oil bath for about 7 h. The product was isolated by the method as described in section 3.1.3. The compounds obtained by both the methods were identical in all aspects (m.p., m.m.p., co-TLC and superimposable IR). Almost similar yields were obtained by both the methods. It was observed that the reaction was simple and accelerated manyfold when carried out in the microwave environment.

Condensation of 2-bromopropionic acid with 2-aminobenzothiazole in the presence of alkali, followed by the reaction of acetic anhydride and pyridine, produced 2-oxo-3-methyl-2,3-dihydroimidazo[2,1-*b*]benzothiazole (**1**) (Ogura and Itoh 1970). Different 1-(chloroalkyl)piperazines (**2**) were prepared by the reaction of 1-bromo-2-chloroethane/1-bromo-3-chloropropane with appropriate piperazines (Santana et al. 2002). Since most of the compounds were obtained in oily/liquid form, they were converted into the corresponding hydrochloride salts by saturating with dry hydrochloride gas. The final compounds were evaluated for their 5-HT_3 antagonistic activities in the LMMP preparation from guinea pig ileum against the 5-HT_3 agonist, 2-methyl-5-HT. The 5-HT_3 antagonism of the title compounds is represented as pA_2 as shown in Table 2. Among the test compounds, **3b** showed higher antagonism (pA_2 6.7) followed by **3c** (pA_2 6.4), whereas standard the antagonist ondansetron showed a pA_2 value of 6.9. Other compounds exhibited mild to moderate antagonistic activity. We observed that when the ethyl linker was used, the title compounds showed higher antagonism compared to those with propyl linker and also compounds with alkyl groups attached to the N^4 piperazine exhibited a higher antagonism than those with aromatic groups.

3. Experimental

3.1. Chemistry

Melting points were determined in open capillaries using a Büchi 530 apparatus, and are uncorrected. Analytical TLC was performed on plates pre-coated with silica gel (Merck 60 F254, 0.25 mm) and the spots were visualized under UV light at 254 and 366 nm. Microwave irradiations were carried out in a domestic microwave oven (LG Electronics, model MG-605AP, 2450 MHz, 900W). IR spectra were recorded in KBr pellets on an IR Prestige-21 FTIR spectrophotometer (cm^{-1}), ^1H NMR spectra on a Bruker DRX300 spectrometer using tetramethylsilane as internal standard (chemical shifts in ä, ppm), mass spectra on a VG-70-S mass spectrometer and elemental analysis on a Perkin Elmer 2400 CHN elemental analyzer.

3.1.1. Synthesis of 2-oxo-3-methyl-2,3-dihydroimidazo[2,1-b]benzothiazole (**1**)

A mixture of 2-aminobenzothiazole (0.05 mol), potassium hydroxide (0.05 mol) and 2-bromopropionic acid (0.05 mol) in ethanol (50 ml) were heated under reflux for 3 h. The solvent was removed under reduced pressure and the resulting yellow syrupy product was heated with acetic anhydride (15 ml) in pyridine (30 ml) for 1 h. The reaction mixture was cooled and poured into ice water. The precipitated material was collected by filtration and recrystallized from ethanol. Yield 44%, m.p. 184–185 °C.

3.1.2. General procedure for the synthesis of 1-(chloroalkyl)-4-substituted piperazine (**2**)

To a stirred solution of piperazine (0.01 mol) in acetone (20 ml) and 25% NaOH (2 ml), 1-bromo-2-chloroethane/1-bromo-3-chloropropane (0.01 mol) was added slowly under ice-cooled conditions. After the addition was completed the reaction mixture was stirred at room temperature for about 48 h. The solvent was removed under reduced pressure and water was added to the residue. The resulting solution was extracted with CH_2Cl_2 (3×10 ml), dried (Na_2SO_4) and evaporated to yield the product, which was converted into its hydrochloride salt and recrystallized from ethanol.

3.1.3. General procedure for the synthesis of 3-[(4-substituted piperazin-1-yl)alkyl]imidazo[2,1-b][1,3]benzothiazol-2(3H)-one (**3**)

To the solution of 2-oxo-3-methyl-2,3-dihydroimidazo[2,1-*b*]benzothiazole (0.005 mol) in ethanol (10 ml) and NaOH (0.01 mol), the appropriate hydrochloride salt of 1-(chloroalkyl)-4-substituted piperazine (0.005 mol) was added. To this mixture neutral alumina (0.5 g) was added. The reaction mixture was thoroughly mixed and dried in the air. It was then placed in an alumina bath and subjected to microwave irradiation, for about 5 min at 900 W. Upon completion of the reaction as monitored by TLC, the reaction mixture was cooled and the product was extracted into CH_2Cl_2 (3×10 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded the product which was recrystallized from a suitable solvent(s). For pharmacological screening, the compounds were converted into their water-soluble hydrochlorides.

3.2. Pharmacology

3.2.1. Evaluation of 5-HT$_3$ antagonism in the LMMP of guinea pig ileum

Experimentation on animals was approved by the Institutional Animal Ethics Committee of the Birla Institute of Technology & Science, Pilani, India. (Protocol No. IAEC/RES/6, dated 21.04.03). The methodology was based on the literature method (Butler et al. 1990). Male Dunkin Hartley guinea pigs (250–300 g; Hissar Agricultural University, Hissar, Haryana, India) were sacrificed by cervical dislocation. The abdomen was cut open and a length of ileum was excised about 2 cm from the ileo-caecal junction. The LMMP, 3–4 cm in length was prepared and mounted (Paton and Zar 1968). The tissue was equilibrated for 30 min under a resting tension of 500 mg and constant aeration in a 40 ml organ bath containing Tyrode solution maintained at ca 37 °C. Non-cumulative concentrations of 2-methyl-5-HT (Tocris, UK) were added with a 15 min dosing cycle (to prevent desensitization) and left in contact with the tissue until the maximal contraction had developed. To study the antagonistic effect of the test compounds on the response evoked by 2-methy-5-HT, the compounds were added to the organ bath and left in contact with the tissue for at least 10 min prior to the addition of 2-methyl-5-HT. The contractions were recorded using a T-305 Force transducer coupled to a Student's physiograph (Bio Devices, Ambala, India). Antagonism was expressed in the form of pA_2 values, which were graphically determined (MacKay 1978). The pA_2 values of the test compounds were compared with the standard antagonist ondansetron (Natco Pharma, Hyderabad, India).

3.3. ^1H NMR spectral study

Compound **1**: δ ($CDCl_3$ + $DMSOd_6$) 2.18–2.21 (d, 3 H, CH_3), 3.01–3.07 (q, 1 H, CH), 7.32–7.37 (t, 1 H, C_7-H), 7.43–7.49 (t, 1 H, C_6-H), 7.75–7.78 (d, 1 H, C_8-H), 7.84–7.87 (d, 1 H, C_5-H).

Compound **2h**: δ ($CDCl_3$, free base) 2.55–2.58 (t, 2 H, N^1CH_2), 2.56–2.59 (t, 4 H, $N^1(CH_2)_2$), 3.01–3.06 (t, 4 H, $N^4(CH_2)_2$), 3.62–3.66 (t, 2 H, CH_2Cl), 3.76 (s, 3 H, OCH_3), 6.70–6.73 (d, 2 H, *m*-OCH_3), 6.83–6.85 (d, 2 H, *o*-OCH_3).

Compound **2w**: δ ($CDCl_3$, free base) 1.95–2.01 (m, 2 H, $CH_2\underline{CH_2}CH_2$), 2.50–2.53 (t, 2 H, N^1CH_2), 2.61–2.65 (t, 4 H, $N^1(CH_2)_2$), 3.41–3.45 (t, 4 H, $N^4(CH_2)_2$), 3.63–3.67 (t, 2 H, CH_2Cl), 6.85–6.87 (d, 2 H, *m*-NO_2), 8.11–8.14 (d, 2 H, *o*-NO_2).

Compound **3b**: δ ($CDCl_3$) 2.18 (s, 3 H, CH_3), 2.26 (s, 3 H, N^4CH_3), 2.35–2.39 (t, 2 H, $\underline{CH_2}CH_2$), 2.42–2.45 (t, 2 H, N^1CH_2), 2.49–2.53 (t, 4 H, $N^4(CH_2)_2$), 2.65–2.69 (t, 4 H, $N^1(CH_2)_2$), 7.36–7.41 (t, 1 H, C_7-H), 7.47–7.51 (t, 1 H, C_6-H), 7.78–7.81 (d, 1 H, C_8-H), 7.89–7.92 (d, 1 H, C_5-H).
Compound **3h**: δ ($CDCl_3$) 2.20 (s, 3 H, CH_3), 2.42–2.46 (t, 2 H, $\underline{CH_2}CH_2$), 2.51–2.55 (t, 2 H, N^1CH_2), 2.72–2.75 (t, 4 H, $N^1(CH_2)_2$), 3.11–3.16 (t, 4 H, $N^4(CH_2)_2$), 3.78 (s, 3 H, OCH_3), 6.76–6.79 (d, 2 H, *m*-OCH_3), 6.85–6.89 (d, 2 H, *o*-OCH_3), 7.37–7.42 (t, 1 H, C_7-H), 7.50–7.55 (t, 1 H, C_6-H), 7.82–7.85 (d, 1 H, C_8-H), 7.93–7.95 (d, 1 H, C_5-H).
Compound **3n**: δ ($CDCl_3$) 2.01–2.07 (m, 2 H, $CH_2\underline{CH_2}CH_2$), 2.21 (s, 3 H, CH_3), 2.27 (s, 3 H, N^4CH_3), 2.43–2.47 (t, 2 H, $\underline{CH_2}CH_2CH_2$), 2.51–2.56 (t, 2 H, N^1CH_2), 2.60–2.65 (t, 4 H, $N^4(CH_2)_2$), 2.72–2.77 (t, 4 H, $N^1(CH_2)_2$), 7.37–7.41 (t, 1 H, C_7-H), 7.47–7.52 (t, 1 H, C_6-H), 7.80–7.83 (d, 1 H, C_8-H), 7.91–7.94 (d, 1 H, C_5-H).

3.4. Mass spectral study

Compound **2h**: m/z = 326 $[M]^+$, 205, 162, 135, 120.
Compound **2w**: m/z = 319 $[M]^+$, 220, 177, 150, 120.
Compound **3b**: m/z = 330 $[M]^+$, 190, 113.
Compound **3h**: m/z = 422 $[M]^+$, 205, 190, 162, 135, 120.
Compound **3n**: m/z = 344 $[M]^+$, 190, 113.

3.5. IR spectral study

Compound **1**: A characteristic IR band at 1687 cm^{-1} and 1591 cm^{-1} indicates a C=O stretch and C=N stretch respectively. Aromatic C−H stretch and C−H bend appears at 3017 cm^{-1} and 750 cm^{-1} respectively.
Compound **2h**: C−N stretch and C−O stretch appears at 1113 cm^{-1} and 1040 cm^{-1} respectively. Aromatic C−H stretch and C−H bend appears at 3040 cm^{-1} and 754 cm^{-1} respectively.
Compound **2w**: Aliphatic C−N stretch appears at 1077 cm^{-1} and $ArNO_2$ shows C−N stretch at 861 cm^{-1}. Aromatic C−H stretch shows peak at 3075 cm^{-1}.
Compound **3b**: Aromatic C−H stretch and C−H bend appears at 3019 cm^{-1} and 769 cm^{-1} respectively. A characteristic band at 1695 cm^{-1} and 1603 cm^{-1} indicates the presence of C=O and C=N respectively. Aliphatic C−N stretch appears at 1125 cm^{-1}.
Compound **3h**: Aromatic C−H stretch and C−H bend appears at 3035 cm^{-1} and 761 cm^{-1} respectively. A characteristic band at 1697 cm^{-1} and 1607 cm^{-1} indicates the presence of C=O and C=N respectively. Aliphatic C−N stretch appears at 1157 cm^{-1}.
Compound **3n**: Aromatic C−H stretch and C−H bend appears at 3023 cm^{-1} and 759 cm^{-1} respectively. A characteristic band at 1683 cm^{-1} and 1611 cm^{-1} indicates the presence of C=O and C=N respectively. Aliphatic C−N stretch appears at 1139 cm^{-1}.

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