Research Article

Environmentally Benign Mortar-Pestle-Induced Acylation and O-Alkylation of Aromatic and Heteroaromatic Compounds under Solvent-Free Micellar Conditions and Computation of Their Drug Likeliness Properties

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Environmentally benign mortar-pestle-induced practical methods have been developed for the acylation and O-alkylation of aromatic and heteroaromatic compounds under solventfree micellar conditions, which were found to efficiently afford moderate to excellent yields of products.

1. Introduction

The diverse nature of chemical universe requires various green strategic pathways in our quest towards attaining sustainability. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. One of the thrust areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized byproducts or waste as well as eliminating the use of conventional organic solvents, wherever possible. Consequently, several newer strategies have appeared such as solvent-free reactions (grinding), multicomponent reactions under solvent-free conditions could enhance their efficiency from an economic as well as an ecological point of view the solid-state organic reactions is gaining significance both from the mechanistic and synthetic point of view [1–3]. Number of articles are available reporting solid-state reactions by grinding such as, Grignard reaction [4], Reformatsky reaction [5], Aldol condensation [6], Dickmann condensation [7], phenol coupling reaction [8], reduction reaction [9], Wittig reaction

[10], Grignard and McMurry reaction [11], and Synthesis of Polyhydroquinolines [12]. In recent past, our research group is actively involved in the exploration of in the exploration of nonconventional methods for nitration, bromination, acetylation, and benzylation reactions in the direction of achieving greenery conditions [13–16]. Most of these grinding reactions are carried out at room temperature, absolutely solvent-free and use only a mortar and pestle and also economical and green procedures. Therefore, we focus on developing the novel procedure involving a solid-state reaction performed by grinding.

Alkylated and acylated aromatic and heteroaromatic compounds are significant precursors in drug intermediates and industrial uses [17]. Specifically naphthalene derivatives such as naphthol ethers and acylated naphthol ethers have been identified as one of the best ranges of potent antimicrobials effective against wide range of human pathogens. A perusal of literature indicated that Williamson synthesis is probably one of the most common classical methods being used for the preparation of symmetrical and unsymmetrical ethers [18–24]. Recent publications of

FIGURE 1: Schematic diagram representing the role of micelles in the reaction.

Swamy et al. [25], Debabrata and coworkers [26, 27], provide excellent bibliography and information on the synthesis of aryl, heteroaryl ethers derived from various roots.

The Friedel-Crafts reaction has a long history in organic synthesis for electrophilic aromatic substitution reactions such as alkylations and acylations. To date these reactions are of great importance for the synthesis of aromatic carbonyl compounds [28]. Aromatic ketones can also be prepared by the reaction of carboxylic acids with aromatic hydrocarbons catalyzed by Nafion-H [29]. A significant number of Lewis acid catalysts (AlCl_3 , FeCl_3 , SnCl_4 , and $\text{BF}_3 \cdot \text{OEt}_2$) have been shown to be very successful for the acylation of aromatic substrates with acid chlorides or anhydrides, while the reaction is usually carried out using a stoichiometric amount of AlCl_3 , reactive aromatic compounds are known to undergo acylation in the presence of a catalytic amount of Lewis acid. Recently, several effective catalyst systems for the acylation of anisole and its derivatives have also been developed [30–34]. A perusal of literature indicated that surfactants have been used to promote a variety of synthetic organic reactions [35–37]. Our preliminary studies in this direction ended up with fruitful results when we have performed the title reactions in presence of micelle forming anionic (SDS), cationic (CTAB, CTAC), and non-ionic (Tx-100) surfactants. This study is aimed at developing “greener synthetic protocols” for etherification and acylation reactions under solvent-free conditions, as encouraged by the “Green Chemistry strategies” of Paul Anastas and Warner [38]. We have used mortar-pestle grinding technique in this study because it is economically cheap and safer method and yet is known to good yields of products in the synthesis of several organic compounds [1–3]. These reactions underwent dramatic rate accelerations under these conditions. We were also successful to develop solvent-free synthetic methods in the above protocols by replacing acids with a variety of micelle forming surfactants such as sodium dodecyl sulphate (SDS), cetyl trimethyl ammonium bromide (CTAB), cetyl trimethyl ammonium chloride (CTAC), and Triton-X 100.

2. Results and Discussion

Synthesis of naphthol ethers under Williamson’s conditions (refluxing in sulfuric acid and organic solvent) required several hours (≥ 20 h) at relatively high temperature. Even though there are some reports to modify the drastic conditions of these reactions, many of them exhibited long reaction times, accumulation of unwanted byproducts, which ultimately involved tedious work-up procedures. Encouraged by this aspect, we have conducted O-alkylation of aromatic and heteroaromatic alcohol reaction (Scheme 1) in micellar media under acid-free conditions.

However, for comparison, we have also conducted etherification of β -naphthol reactions under Williamson’s classical conditions in acidic media. Results obtained under acidic and acid-free micellar conditions are compiled in Table 1 and O-alkylation of hydroxy pyridines in Table 2, and the reaction time versus conversion of aromatic/heteroaromatic alcohols using micelles as a catalyst were reported in Table 3, which clearly indicate highly significant rate accelerations followed by very good yield of end products. Catalytic activity of different micelles is in the order: CTAB > SDS > Tx-100. It is believed that micelles themselves act as micro-reactors. By introducing a surfactant (CTAB), dehydration was successfully achieved. The catalytic effect of the micellar solution of CTAB may be attributed to the hydrophobic nature of organic substrates. Formation of emulsion droplets takes place in water in the presence of surfactant and substrate molecules. It is suggested that most of the organic substrates are concentrated in these spherical droplets, which act as a hydrophobic reaction sites and results in an increase in the effective concentration of the organic reactants, which might increase the reaction rate via a concentration effect. In micellar solution, organic substrates are pushed away from water molecules towards the hydrophobic core of micelle droplets thus inducing efficient collisions between organic substrates which eventually enhance the reaction rates. The hydrophobic interior of the micelles swiftly excludes the water molecules generated during the reaction, thus shifting the equilibrium towards the desired product that ultimately

FIGURE 2: Schematic diagram representing the role of CTAB in the reaction.

SCHEME 1: O-alkylation of Aromatic/heteroaromatic compounds in micellar media.

leads to an increase in the reaction yield [39, 40]. This explanation is schematically represented in Figures 1 and 2.

The Friedel-Crafts acylation of 2-methoxy naphthalene in the presence of the electron-donating group (OMe) must be taken into account in order to figure out the reaction. Presence of the electron-donating group activates the 1, 6, and 8 positions of the naphthalene ring.

The 1-position is more active than the other two positions and the 6-position is more stable than the other two positions, so acylation of 2-methoxynaphthalene generally occurs at this kinetically favoured 1-position at low temperatures and at the thermodynamically favoured 6-position at high temperatures. At high temperatures, in the reaction mixture, migration of the acyl group from 1- to 6-position which is named as transacylation and protideacylation of the acyl group at the 1-position of 1-acyl-2-methoxy naphthalene are possible. These two reactions may result in the formation of the thermodynamically favoured product which is 6-acyl-2-methoxynaphthalene. Steric hindrance to acylation is reported in the order 1 > 8 > 6-position (Das, 2000). Therefore, the isomerisation of the sterically hindered ketone 1-acyl-2-methoxynaphthalene to sterically less hindered isomers like 6-acyl-2-methoxy naphthalene and 8-acyl-2-methoxynaphthalene will be favoured.

Catalytic reaction of 1-halo-2-methoxy naphthalene (2 mmol) was treated with acylchloride (2 mmol) in the

TABLE 1: Mortar-pestle-induced O-alkylation of β -naphthols under solvent-free conditions.

Reactants		H ₂ SO ₄ (5 hr)	CTAB (2 hr)	SDS (2.5 hr)	TX-100 (3.0 hr)	M.P/B.P (°C)
1	2	% yield	% yield	% yield	% yield	
β -Naphthol	MeOH	89	93	90	90	70-71
	EtOH	90	93	90	90	35-37
	1-PrOH	88	91	91	91	37-39
	2-PrOH	91	94	91	91	—
1-Bromonaphthalen-2-ol	MeOH	90	91	89	90	80-81
	EtOH	88	92	90	90	64-66
	1-PrOH	88	96	90	89	—
	2-PrOH	91	94	89	89	37-39
1-Chloronaphthalen-2-ol	MeOH	90	90	93	89	64-65
	EtOH	90	90	92	90	56-58
	1-PrOH	91	91	91	88	—
	2-PrOH	91	91	94	91	—
1-Iodonaphthalen-2-ol	MeOH	90	89	91	90	87-89
	EtOH	90	90	92	88	35-37
	1-PrOH	89	90	96	88	37-39
	2-PrOH	89	89	94	91	—

SCHEME 2: Acylation of 1-halo-2-methoxy naphthalenes in micellar media.

presence of CTAB or CTAC, (0.1 mmol, 5 mol%) were grounded with pestle for 2 hr it gave 6-acyl-1-halo-2-methoxynaphthalene(3) as the major product along with 8-acyl-1-halo-2-methoxy naphthalene(4) selectivity (98 : 02) represented as in Scheme 2, Table 4 and the reaction time versus conversion of 1-halo-2-methoxy naphthalenes using CTAB/CTAC (various amounts) as a catalyst were reported in Table 5.

Mortar-pestle grinding synthetic methods were to avoid solvent. The reaction times fairly reduced from 24 h to about 2-3 h (under Williamson's method to Mortar-pestle method) without many changes in the yield of products (Tables 1 and 2). Rate accelerations under grinding method could be attributed to bulk activation of molecules due to the conversion of mechanical energy (exerted due to grinding) into heat energy due to frictional forces operating between solid state reagents [1-3].

2.1. Calculation of Molecular Physicochemical Properties by Molinspiration. Drug likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility, and various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability, and many others. Mol inspiration calculations are a set of simple molecular properties obtained by Lipinski Rule-5 of 5'' [41, 42], which are useful to explore drug likeness nature of a molecule. Lipinski's fifth rule states that a molecule possess "drug-likeness" if the molecule has the properties: $\log P \leq 5$, molecular weight ≤ 500 , number of hydrogen bond acceptors ≤ 10 , and number of hydrogen bond donor's

TABLE 2: Mortar-pestle-induced micellar mediated O-alkylation of hydroxy pyridines under solvent-free conditions.

Reactants		CTAB (1.5 hr)	SDS (2.0 hr)	TX-100 (2.5 hr)
1	2	% yield	% yield	% yield
2-Hydroxy pyridine	MeOH	89	85	86
	EtOH	90	87	87
	1-PrOH	90	86	82
	2-PrOH	90	87	89
3-Hydrox pyridine	MeOH	91	85	82
	EtOH	89	84	81
	1-PrOH	85	83	80
	2-PrOH	89	85	79
4-Hydroxy pyridine	MeOH	91	88	81
	EtOH	88	85	83
	1-PrOH	88	83	82
	2-PrOH	89	84	81
5-Bromopyrimidin-2-ol	MeOH	91	87	89
	EtOH	89	87	87
	1-PrOH	89	86	86
	2-PrOH	91	84	86
6-Hydroxypicolinaldehyde	MeOH	92	88	89
	EtOH	88	86	89
	1-PrOH	87	85	84
	2-PrOH	88	87	86

≤ 5 . Molecules violating more than one of these rules may have problems with bioavailability. For the prediction of oral bioavailability of drug molecules [43], lipophilicity ($\log P$ value), and polar surface area (PSA) [44] values are the most important properties. The Calculated parameters from Mol inspiration methodology for each newly synthesized 6-acyl-1-halo-2-methoxynaphthalene derivative (entries 1 to 14) are compiled in Tables 6 and 7 and tested for specific activity with standard drugs Naproxen. For all the compounds, the calculated $\log P$ values were ≤ 5 (in comparison with the accepted the upper limit) indicating the ability of the drug to penetrate through biomembranes and also good water solubility (according to Lipinski's rules). Further it is also interesting to note that all the synthesized molecules exhibit less than 140 PSA values indicating good intestinal absorption. Data presented in Table 7 are GPCR ligand activity, ion channel modulation, kinase inhibition activity, nuclear receptor ligand activity, Protease inhibitor, and Enzyme inhibitor are compared with Naproxen as standard drug indicate that most of the synthesized compounds depict by and large consistent negative values, which are in consonance with Lipinski's Rule -5 and are also comparable with Naproxen drug.

3. Conclusions

There are different shades of greener processes as we continue exploring several alternatives to conventional chemical transformations. That approach will require new environmentally benign syntheses of O-alkylation and acylation of naphthalene derivatives in aqueous micellar media. Thus, the present protocols show rate accelerations associated with high products yields, when compared with the similar reactions performed under classical conditions. Surfactants catalyze the reaction efficiently with short reaction times without using any harmful organic reagents and solvents. Molecular properties computed from Molinspiration methodology for all the synthesized 6-acyl-1-halo-2-methoxynaphthalene derivatives by and large indicate Drug likeliness behavior that is comparable to standard drugs. Thus, it is believed that the present work is a major breakthrough in the area of synthesis of 6-acyl, 1-halo-2-methoxy naphthalenes with potential biological activity.

4. Experimental Details

All reactions were followed by TLC with detection by UV light. Melting points were recorded on BUCHI B-545 capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded at a Varian VNMR-400 and 100 MHz spectrometer. The Samples were analyzed in CDCl_3 , DMSO- d_6 chemical shift values are reported in ppm relative to TMS as the internal reference. Mass spectra were recorded on a ZAB-HS mass spectrometer using ESI ionization. The isolation of pure products was carried out via preparative thin layer chromatography (silica gel 60 GF₂₅₄, Merck). Excess of solvent was evaporated under reduced pressure at a bath temperature of 50°C. All solvents, organic and inorganic compounds, were purchased from Aldrich, Merck, Fluka, and Sdfine and used without further purification.

4.1. General Procedure for Etherification of β -Naphthols under Mortar Pestle Conditions. A mixture of substrate (10 mmol), alcohol (20 mmol), and micelles (1.0 mmol, 25 mol %) were added to a mortar. The mixture was grounded by mortar and pestle at room temperature, after the indicated reaction time, the reaction mixture was purified by thin layer chromatography (silicagel, EtOAc-petroleum ether, 1 : 9) to obtain the desired product.

4.2. General Procedure for Acylation of β -Naphthols under Mortar Pestle Conditions. 1-halo-2-methoxynaphthalene (2 mmol) and acylchloride (2 mmol) and CTAB (0.1 mmol, 5 mol %) were added to a mortar and grinded with pestle till the reaction is completed as ascertained by TLC. The final products were isolated by absorbing the reaction mixture into silica gel and purifying it by column chromatography using ethyl acetate/hexane gradient.

TABLE 3: Reaction of aromatic/heteroaromatic alcohol (10 mmol) with methanol (20 mmol) using micelles as catalysts.

Aromatic/heteroaromatic alcohol (1)	CTAB		SDS		TX-100	
	Time (min)	Conversion of 1 (%)	Time (min)	Conversion of 1 (%)	Time (min)	Conversion of 1 (%)
β -Naphthol	60	50	60	50	60	45
	80	63	90	65	100	60
	100	75	120	75	140	78
	120	93	150	90	180	90
2-Hydroxy pyridine	60	60	60	55	60	50
	70	73	90	68	90	65
	80	81	120	77	120	77
	90	89	120	85	150	86

4.3. Spectroscopic Analysis of Representative Compounds

2-Methoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 3.91 (s, 3H), 7.15–7.17 (d, $J = 8.8$ Hz, 1 H), 7.29–7.36 (m, 2H), 7.43–7.47 (m, 1H), 7.72–7.77 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 55.6, 105.9, 113.7, 124.4, 126.2, 127.8, 128.2, 129.1, 129.9, 133.2, 153.8; IR (KBr, cm^{-1}) 3067, 3008, 2963, 1632, 1599, 1477, 1462, 1452, 1440, 1398, 1391, 1368, 1262, 1218, 1197, 1173, 1152, 1141, 1118, 1031, 1017, 963, 948, 874, 838, 818, 753, 743, 622, 481, 470; MS (EI) m/z 159.2 (M) $^+$.

2-Ethoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 1.46 (t, $J = 7.2$ Hz, 3H), 4.127 (d, $J = 6.8$ Hz, 2H), 7.14–7.15 (d, $J = 8.8$ Hz, 1H), 7.28–7.39 (m, 2H), 7.39–7.43 (m, 1H), 7.69–7.75 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 14.8, 64.1, 106.5, 118.9, 123.4, 126.2, 126.7, 128.2, 129.1, 129.2, 133.6, 156.8; IR (KBr, cm^{-1}) 3067, 2984, 2940, 2876, 1829, 1601, 1579, 1511, 1457, 1440, 1395, 1390, 1367, 1358, 1350, 1269, 1259, 1185, 1166, 1144, 1122, 1046, 1020, 958, 928, 873, 823, 762, 719, 623, 477; MS (EI) m/z 173.2 (M) $^+$.

2-Propoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 1.06 (t, $J = 6.0$ Hz, 3H), 1.83–1.86 (m, 2H), 4.01 (t, 2H), 7.10–7.14 (m, 2H), 7.30–7.41 (m, 2H), 7.69–7.74 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 10.5, 22.6, 69.4, 106.6, 119.1, 123.4, 126.2, 126.6, 127.6, 128.8, 129.3, 134.6, 156.7; IR (KBr, cm^{-1}) 3060, 2976, 2934, 2908, 2878, 1948, 1904, 1832, 1628, 1600, 1513, 1479, 1467, 1448, 1441, 1392, 1371, 1357, 1270, 1260, 1216, 1146, 1121, 1046, 1024, 1017, 1017, 986, 958, 916, 842, 819, 770, 746, 727, 727, 645, 623, 474; MS (EI) m/z 187.10 (M) $^+$.

2-Isopropoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 1.45 (d, $J = 6.0$ Hz, 6H), 4.66–4.82 (m, 1H), 7.13–7.18 (m, 2H), 7.28–7.48 (m, 2H), 7.68–7.82 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 22.0, 69.8, 108.4, 119.7, 123.4, 126.2, 126.6, 127.6, 128.8, 129.3, 134.6, 155.7; IR (KBr, cm^{-1}) 3580, 2981, 2936, 2876, 1948, 1904, 1832, 1628, 1600, 1581, 1510, 1468, 1440, 1388, 1373, 1356, 1334, 1216, 1188, 1171, 1137, 1118, 1019, 974, 941, 900, 871, 842, 814, 675, 645, 623, 532; MS (EI) m/z 187.10 (M) $^+$.

1-Chloro-2-methoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 4.03 (s, 3H), 7.25 (d, $J = 8.6$ Hz, 1H), 7.37–7.52 (m, 1H), 7.53–7.61 (m, 1H), 7.79–7.69 (m, 2H), 8.25 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ 57, 105.9, 113.7, 124.4, 126.2, 127.8, 128.2, 129.1, 129.9, 133.2, 153.8; IR (KBr, cm^{-1}) 3430, 3049, 2972, 2948, 2846, 2541, 1948, 1763, 1625, 1590, 1505, 1469, 1355, 1337, 1273, 1246, 1187, 1148, 1068, 1018, 985, 894, 865, 804, 764, 740, 657, 588, 532; MS (EI) m/z 192 (M) $^+$.

1-Bromo-2-methoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 4.04 (s, 3H), 7.28 (d, $J = 8.6$ Hz, 1H), 7.39–7.53 (m, 1H), 7.53–7.61 (m, 1H), 7.76–7.89 (m, 2H), 8.23 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ 57.1, 105.9, 113.7, 124.4, 126.2, 127.8, 128.2, 129.1, 129.9, 133.2, 153.8; IR (KBr, cm^{-1}) 3430, 3045, 2970, 2941, 2841, 1620, 1594, 1500, 1466, 1454, 1351, 1334, 1270, 1245, 1185, 1153, 1134, 1061, 1021, 968, 890, 855, 803, 761, 743, 708, 644, 579, 516 cm^{-1} ; MS (EI) m/z (M-H) $^+$ 236.10.

1-Iodo-2-methoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 4.03 (s, 3H), 7.22 (d, $J = 9.0$ Hz, 1H), 7.34–7.42 (m, 1H), 7.50–7.56 (m, 1H), 7.75 (d, $J = 8.6$ Hz, 1H), 7.84 (d, $J = 9.0$ Hz, 1H), 8.15 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ 57.3, 87.8, 113.0, 124.4, 128.2, 128.3, 130.4, 131.3, 130.0, 135.7, 156.7; IR (KBr, cm^{-1}) 3042, 3006, 2969, 2937, 2838, 1617, 1587, 1551, 1497, 1451, 1423, 1346, 1328, 1263, 1242, 1181, 1153, 1132, 1058, 1021, 959, 887, 801, 761, 743; MS (EI) m/z 285.06 (M) $^+$.

1-Bromo-2-ethoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 1.38–1.41 (t, $J = 6.8$ Hz, 3H), 4.13–4.14 (q, $J = 6.8$ Hz, 2H), 7.15–7.17 (d, $J = 8.8$ Hz, 1 H), 7.29–7.36 (m, 2H), 7.43–7.47 (m, 1H), 7.78–7.83 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 22.8, 64.6, 105.9, 113.7, 124.4, 126.2, 127.8, 128.2, 129.1, 129.9, 133.2, 153.8.

1-Bromo-2-propoxynaphthalene. ^1H NMR (400 MHz, CDCl_3) δ 1.03 (t, $J = 7.5$ Hz, 3H), 1.80–1.86 (m, 2H), 4.51 (t, 7.5 Hz, 2H), 7.10–7.14 (m, 2H), 7.30–7.41 (m, 2H), 7.69–7.74 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 10.5, 22.6,

TABLE 4: Reaction of 1-halo-2-methoxy naphthalene (2 mmol) with acylchlorides (2 mmol) using CTAB/CTAC as a catalyst.

Naphthalene	Acylchloride	Total (%) Yield	Products ratio (3:4)
1a	2a	93	98:02
1a	2b	90	98:02
1a	2c	89	98:02
1a	2d	92	98:02
1a	2e	90	98:02
1a	2f	93	98:02
1a	2g	94	98:02
1b	2a	93	97:03
1b	2b	90	98:02
1b	2c	89	98:02
1b	2d	92	98:02
1b	2e	90	98:02
1b	2f	93	98:02
1b	2g	94	98:02

Duration of all reactions was 2 hr.

78.4, 113.6, 123.4, 126.2, 126.6, 127.6, 128.8, 129.3, 131.3, 132.6, 154.7; MS (EI) m/z 266.04 (M)⁺.

1-Bromo-2-isopropoxy Naphthalene. ¹H NMR (400 MHz, CDCl₃) δ 1.45 (d, J = 6.0 Hz, 6H), 4.61–4.87 (m, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.39–7.53 (m, 1H), 7.53–7.61 (m, 1H), 7.76–7.85 (m, 2H), 8.23 (d, J = 8.6 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃) δ 22.0, 69.8, 108.4, 119.7, 123.4, 126.2, 126.6, 127.6, 128.8, 129.3, 134.6, 155.7; IR (KBr, cm⁻¹) 3580, 2981, 2936, 2876, 1948, 1904, 1832, 1628, 1600, 1581, 1510, 1468, 1440, 1388, 1373, 1356, 1334, 1216, 1188, 1171, 1137, 1118, 1019,

TABLE 5: Reaction of 1-halo-2-methoxynaphthalene (2 mmol) With 2g (2 mmol) using CTAB/CTAC (various amounts) as a catalyst.

Naphthalene	CTAB/CTAC (mmol)	Time (min)	Conversion of 1 (%)
1a	0.02	60	70
		80	73
		100	75
		120	80
1a	0.04	60	72
		80	78
		100	82
		120	85
1a	0.06	60	74
		80	80
		100	84
		120	86
1a	0.08	60	76
		80	83
		100	86
		120	90
1a	0.10	60	80
		80	85
		100	89
		120	93
1b	0.02	60	70
		80	75
		100	78
		120	83
1b	0.04	60	72
		80	75
		100	79
		120	85
1b	0.06	60	74
		80	79
		100	80
		120	87
1b	0.08	60	76
		80	81
		100	83
		120	89
1b	0.10	60	80
		80	85
		100	88
		120	93

974, 941, 900, 871, 842, 814, 675, 645, 623, 532; MS (EI) m/z 266.10 (M)⁺.

4-Methoxy Pyridine. ¹H NMR (400 MHz, CDCl₃) δ 3.84 (s, 3H), 6.81 (d, J = 8.6 Hz, 2H), 8.43 (d, J = 8.6 Hz, 1H); ¹³C

TABLE 6: Molinspiration calculations of compounds.

S. number	6-Acyl-1-halo-2-methoxynaphthalene	M.Wt	miLog <i>P</i>	TPSA	OH-NH	<i>n</i> -Vio	Volume
1	1-(1-Bromo-2-methoxynaphthalen-6-yl)ethanone	279.13	3.789	26.305	0	2	0
2	1-(1-Bromo-2-methoxynaphthalen-6-yl)pentan-1-one	321.21	5.356	26.305	0	2	1
3	1-(1-Bromo-2-methoxynaphthalen-6-yl)hexan-1-one	335.24	5.861	26.305	0	2	1
4	1-(1-Bromo-2-methoxynaphthalen-6-yl)-4-methylpentan-1-one	335.24	5.337	26.305	0	2	1
5	1-(1-Bromo-2-methoxynaphthalen-6-yl)-5-methylhexan-1-one	349.26	5.842	26.305	0	2	1
6	1-(1-Bromo-2-methoxynaphthalen-6-yl)-3,3-dimethylbutan-1-one	335.24	5.386	26.305	0	2	1
7	1-(1-Bromo-2-methoxynaphthalen-6-yl)-2-phenylethanone	355.23	5.217	26.305	0	2	1
8	1-(1-Chloro-2-methoxynaphthalen-6-yl)ethanone	234.68	3.658	26.305	0	2	0
9	1-(1-Chloro-2-methoxynaphthalen-6-yl)pentan-1-one	276.76	5.225	26.305	0	2	1
10	1-(1-Chloro-2-methoxynaphthalen-6-yl)hexan-1-one	290.79	5.73	26.305	0	2	1
11	1-(1-Chloro-2-methoxynaphthalen-6-yl)-4-methylpentan-1-one	290.79	5.206	26.305	0	2	1
12	1-(1-Chloro-2-methoxynaphthalen-6-yl)-5-methylhexan-1-one	304.81	5.711	26.305	0	2	1
13	1-(1-Chloro-2-methoxynaphthalen-6-yl)-3,3-dimethylbutan-1-one	290.79	5.255	26.305	0	2	1
14	1-(1-Chloro-2-methoxynaphthalen-6-yl)-2-phenylethanone	310.78	5.086	26.305	0	2	1
STD	Naproxen	264.70	3.983	46.533	1	3	0

TABLE 7: Drug likeness of compounds.

S. number	6-Acyl-1-halo-2-methoxynaphthalene	GPCRL	ICM	KI	NRL
1	1-(1-Bromo-2-methoxynaphthalen-6-yl)ethanone	-0.56	-0.51	-0.71	-0.57
2	1-(1-Bromo-2-methoxynaphthalen-6-yl)pentan-1-one	-0.18	-0.36	-0.42	-0.20
3	1-(1-Bromo-2-methoxynaphthalen-6-yl)hexan-1-one	-0.13	-0.34	-0.35	-0.14
4	1-(1-Bromo-2-methoxynaphthalen-6-yl)-4-methylpentan-1-one	-0.14	-0.33	-0.39	-0.14
5	1-(1-Bromo-2-methoxynaphthalen-6-yl)-5-methylhexan-1-one	-0.09	-0.31	-0.34	-0.08
6	1-(1-Bromo-2-methoxynaphthalen-6-yl)-3,3-dimethylbutan-1-one	-0.19	-0.27	-0.46	-0.32
7	1-(1-Bromo-2-methoxynaphthalen-6-yl)-2-phenylethanone	-0.06	-0.30	-0.24	-0.05
8	1-(1-Chloro-2-methoxynaphthalen-6-yl)ethanone	-0.50	-0.22	-0.67	-0.49
9	1-(1-Chloro-2-methoxynaphthalen-6-yl)pentan-1-one	-0.13	-0.12	-0.39	-0.14
10	1-(1-Chloro-2-methoxynaphthalen-6-yl)hexan-1-one	-0.08	-0.11	-0.32	-0.08
11	1-(1-Chloro-2-methoxynaphthalen-6-yl)-4-methylpentan-1-one	-0.10	-0.10	-0.37	-0.08
12	1-(1-Chloro-2-methoxynaphthalen-6-yl)-5-methylhexan-1-one	-0.04	-0.09	-0.31	-0.02
13	1-(1-Chloro-2-methoxynaphthalen-6-yl)-3,3-dimethylbutan-1-one	-0.14	-0.04	-0.43	-0.26
14	1-(1-Chloro-2-methoxynaphthalen-6-yl)-2-phenylethanone	-0.02	-0.10	-0.21	0.00
STD	Naproxen	-0.06	0.00	-0.36	0.18

GPCR: ligand, ICM: Ion channel modulator, KI: Kinase inhibitor, NRL: Nuclear receptor ligand.

NMR (50 MHz, CDCl₃) δ 55.1, 109.9, 151.4, 165.4, MS (EI) m/z 110.3(M)⁺, (B.P.168.2°C).

4-Ethoxy Pyridine. ¹H NMR (400 MHz, CDCl₃) δ 1.34 (q, 2H), 3.94 (t, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 8.4 Hz, 2H); MS (EI) m/z 123.8(M)⁺, (B.P.165°C).

3-Methoxy Pyridine. ¹H NMR (400 MHz, CDCl₃) δ 3.84 (s, 3H), 7.34 (t, *J* = 8.65, *J* = 4.75 Hz, 1H), 7.38 (d, *J* = 8.65 Hz, 1H); 8.19 (d, *J* = 4.75 Hz, 1H); 8.32 (s, 1H); MS (EI) m/z 110.3(M)⁺, (B.P.168.4°C).

6-Methoxypicolinaldehyde. ¹H NMR (400 MHz, DMSO) δ 3.971 (s, 3H), 6.986 (d, *J* = 8.3 Hz, 1H), 8.108–8.136 (m, 1H), 8.770 (d, *J* = 2.5 Hz, 1H); 9.968 (s, 1H); MS (EI) m/z 137.9(M)⁺.

2-Methoxy Pyridine. ¹H NMR (400 MHz, CDCl₃) δ 3.94 (s, 3H), 6.72 (d, *J* = 8.65 Hz, 1H); 6.82 (t, *J* = 8.65, *J* = 4.75 Hz, 1H), 7.59 (t, *J* = 8.65, *J* = 4.75 Hz, 1H); 8.18 (d, *J* = 4.75 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃) δ 53.1, 110.9, 116.4, 138, 147, 165.4, MS (EI) m/z 110.3 (M)⁺, (B.P.142.5°C).

5-Bromo-2-methoxypyrimidine. ¹H NMR (400 MHz, DMSO) δ 3.915 (s, 3H), 8.765 (s, 2H); MS (EI) m/z 188.9(M)⁺.

1-(5-Bromo-6-methoxynaphthalen-2-yl)hexan-1-one. ¹H NMR (400 MHz, CDCl₃) δ 0.95 (t, *J* = 6.6 Hz, 3H),

1.38–1.42 (m, 4H), 1.93 (d, $J = 7.7$ Hz, 2H), 3.03 (t, $J = 7.7$ Hz, 2H), 4.02 (s, 3H), 7.28 (d, $J = 8.7$ Hz, 1H), 7.98 (d, $J = 8.7$ Hz, 1H), 8.04 (s, 1H), 8.23 (d, $J = 8.7$ Hz, 1H), 8.41 (d, $J = 8.7$ Hz, 1H); IR (KBr) 3430, 3057, 3016, 2957, 2922, 2882, 2126, 1943, 1716, 1672, 1621, 1559, 1492, 1472, 1440, 1408, 1357, 1328, 1272, 1252, 1219, 1177, 1065, 965, 908, 863, 822, 801, 768, 732, 663, 596, 520, 467 cm^{-1} ; MS (ES) m/z (337.0 M) $^{+2}$.

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