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Solvent Free One Pot Microwave Synthesis of Quinazolin 4-(3*H*)-One Derivatives with their Antibacterial and Antifungal Activity.

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Abstract : Since long time, quinazoline and their derivatives are found to be active for the synthesis of various categories of drugs. The 2, 3-di-substituted quinazolin-4-(3H)-ones (III) and its derivatives have been synthesized as a one pot procedure from the reaction of Anthranilic acid (I), acid chlorides and different primary amines with the intermediate 4-(3H)-benzoxazinone (II) at different microwave conditions. High yield, less by products, short reaction time (7 to10 min), mild conditions and easy work-up are the advantages of this methodology. The pure compounds are separated through the preparative TLC method and using hydro-alcoholic solution. The final derivatives are characterized by UV, IR, Mass, NMR and screened for antimicrobial and antibacterial activity.

Keywords: Microwave assisted synthesis, one pot synthesis, 2, 3-di-substituted quinazolin-4-(3H)-ones, antimicrobial activity.

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INTRODUCTION

Microwave assisted organic synthesis (MAOS) has emerged as frontier in pharmaceutical research for synthesis of newer drugs. MAOS help not only in implementing GREEN chemistry but also led to the revolution in organic synthesis[1]. The quinazoline skeleton appears in many alkaloids, most commonly in the form of 4-(3H)-quinazolinone[2]. The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities. Like benzodiazepines, the quinazolines are considered to be a "privileged structure" for drug development[3, 4]. Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects, useful to inhibit tumor growth[5]. This has recently inspired the development of a new ring synthesis method.

The 4-(3H)-quinazolinones are the formal condensation products of Anthranilic acid and amides, and they can also be prepared in this fashion through the *Niementowski quinazolinone synthesis*[6,7]. With wide applications including anticonvulsant[8], sedative, tranquilizer, analgesic[9, 10], antimicrobial[11], anesthetic[12], anticancer[13], antihypertensive[14], anti-inflammatory[15], diuretic[16] and muscle relaxant properties[17]. The utility in material science is due to their luminescent and thermal stability. 2, 3-di-substituted quinazolin-4-(3H)-one have been prepared by different methods like condensation of Anthranilic acid with acid amides, condensation of acetanilide with urethanes, condensation of N-acyl Anthranilic acids with primary amines[18]. A recent paper has reported a 3-catalyzed one pot synthesis of quinazolin-4-(3*H*)-one from Anthranilic acid, anilines and ortho esters (or formic acid) under solvent-free conditions, but the method seems to be restricted to the synthesis of 2-aryl substituted quinazolin-4-(3*H*)-one[19].

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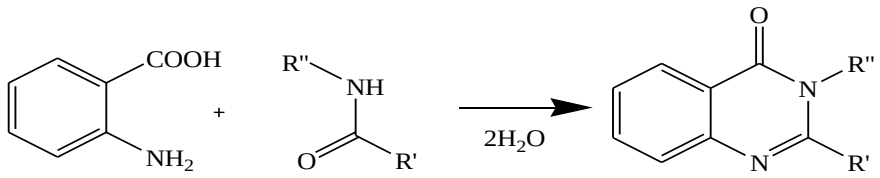

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MATERIALS AND METHODS

Experimental

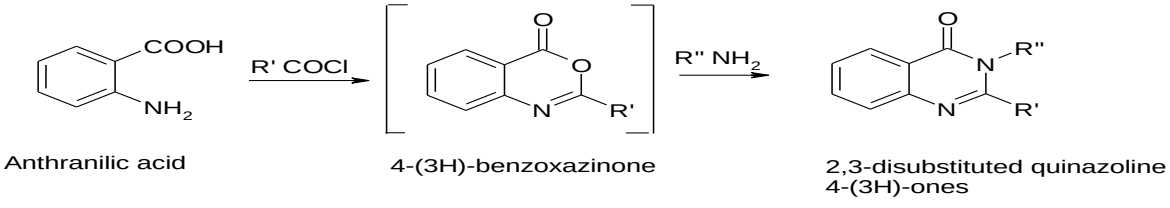
Distillation of solvents and acid chloride was done with distillation assembly in laboratory. For synthesis CATA's scientific microwave system, RG 31L with power output 700 W, 2450 MHz been used. Melting points were taken on DBK programmed melting point apparatus. Anthranilic acid, aniline and 3-amino phenol was purchased from S.D. Fine Chemicals, Mumbai and methyl amine and ethyl amine was purchased from LOBA chemicals, Mumbai. Silica gel G Plates (3x8cm) were used for TLC and spots were located by U.V. chamber.

IR spectra were taken with 8400 S, Shimadzu Corporation (KBr) and the values expressed in cm^{-1}. ^1H NMR spectra ($CDCl_3$) were taken on AVANCE-300, (300MHz FT NMR). U.V. Spectra were taken on U.V. 401 (PC) S 220V Double beam U.V. spectrophotometer. CHN analysis were taken with perkin-elmer, 2400, series-II.

2, 3 Di-substituted Quinazolinone: Equimolar amount of Anthranilic acid (1.37 g) (0.8), (acid chloride)-benzoyl chloride (1.40 ml) (0.7)/ propionyl chloride (0.92 ml) (0.4)/ acetyl chloride (0.78 ml) (0.6) and aniline (0.93 ml) (0.06)/ 3-aminophenol (1.9 g) (0.7)/ 2-amino pyridine (0.94 gm) (0.09)/ Methyl amine (0.31) (0.04)/ Ethyl amine (0.46) (0.05) were placed in 150 ml two necked flask. The mixture was refluxed by microwave irradiation in scientific microwave oven at reflux temperature (power input: 560 W, 9 P) for 07 min (aniline)/ for 10 min (methyl amine, ethyl amine, 3-aminophenol and 2-amino pyridine), gives the product quinazolinone **(III a – III h)**.

After cooling the flask, required quantity of ethanol (96%) was added and then mixed thoroughly. Solution was poured in beaker containing crushed ice and little amount of conc. hydrochloric acid. The solid separated was filtered, dried and recrystallized from ethanol. For further purity, the product **(III c), (III d), (III e) and (III g)** was recrystallized in hydro-alcoholic solution. The product **(III a)**, **(III b), (III f) and (III h)** was finally purified by preparative thin layer chromatography using ethyl acetate: n-hexane as mobile phase in the ratio of 3:7.

All the obtained products were >96% pure as found by TLC and ^1H NMR analysis and MS. The physicochemical characteristics and spectral data of various compounds **(III a-III h)** are given in **Table 1**



(I) (II) (III)

[R' = Acetyl, Benzyl and propyl; R'' = Phenyl; 3-Hydroxy Phenyl; Pyridine, methyl, ethyl.]

[Scheme – 1]

(III-a) 2-ethyl-3-phenylquinazolin-4-(3H)-one

UV: The absorption maxima at 225.80 nm in methanol. ***IR (KBr) cm^{-1}***: 1681.81 C=O str, 3058.13 (Ar C-H Str), 2920.03 aliphatic C-H stretching, 1608.52 C=N str; ***^{1}H NMR (300 MHz, DMSO-d$_6$)***: 1.16-1.20 (m CH_3), 2.15-2.35 (s Ar-H), 2.02 (m Ar-H), 7.30 – 7.43, 7.54 – 7.68, 7.71 – 7.83, 7.85 – 7.86, 8.09 – 8.12 (m Ar-H). ***CHN analysis calculated %:*** C, 76.08; H, 5.81; N, 11.02; found C, 75.12; H, 5.81; N, 11.10**.** ***MS (m/z)***: 60, 77 102, 118, 134, 144, 158, 173, 250.

(III-b) 2, 3-diphenylquinazolin-4-(3H)-one

UV: The absorption maxima at 239.20 nm in methanol. ***IR (KBr) cm^{-1}***1685.67 C=O str, 3072.17 Ar-CH str, 1608.52 C=N str. ***^{1}H NMR (300 MHz, DMSO-d$_6$)***: 2.49-2.60 (s Ar-H), 3.33-3.65 (s CH_2), 6.01 – 6.82 , 7.0 – 8.56, 1.97 – 2.22 (m Ar-H). ***CHN analysis calculated %***: C, 80.53; H, 4.69; N, 09.39; found C, 80.73; H, 4.40; N, 09.50. ***MS (m/z)*:** 50, 76, 103, 119, 143, 221, 298.

(III-c) 3-(3-hydroxyphenyl)-2-phenylquinazolin-4-(3H)-one

UV: The absorption maxima at 224.80 nm in methanol. ***IR (KBr) cm^{-1}*** 1680 (C=O str), 3034 (Ar-C-H str), 1598.88 (Aromatic C⎓C str), 1608.42 (C=N str). ***^{1}H NMR (300 MHz, DMSO-d$_6$)***, 2.14–2.30 (s Ar-H), 1.20 – 1.25 (m OH), 2.50 – 2.55 (m Ar-H), 6.80 – 6.82, 6.88 – 6.90, 7.30 – 7.36, 7.46 – 7.47, 8.06 – 8.09 (m Ar-H). ***CHN analysis calculated %*:** C, 76.43; H, 4.45; N, 8.91; found C, 75.98; H, 4.73; N, 08.76. ***MS (m/z)***: 50, 76, 103, 117, 145, 222, 297, 314.

(III-d) 2-ethyl, 3-pyridine-2ylquinazolin-4-(3H)-one

UV: The absorption maxima at 215.02 nm in methanol. ***IR (KBr) cm^{-1}***, 1683.74 C=O str, 3064.68 Ar-C-H str, 1604.66 C=N str. ***^{1}H NMR (300 MHz, DMSO-d$_6$)***: 6.01 – 7.06, 7.98 – 8.06 (m Ar-H), 1.17 – 1.30 (m CH_3), 2.49 – 2.55, 3.20 – 3.65 (s Ar-H), 2.02 (m Ar-H). ***CHN analysis calulated %***: C, 71.71; H, 5.17; N, 16.71; found C, 71.25; H, 5.09; N, 16.12. ***MS (m/z)***: 57, 76, 92, 144, 157, 173, 251.

(III-e) 2-methyl-3-phenylquinazolin-4-(3H)-one:

UV: The absorption maxima at 225.80 nm in methanol. ***IR (KBr) cm^{-1}***, 1681.81, 3058.13, 2920.03, 1608.52; ***^{1}H NMR (300 MHz, DMSO-d$_6$)***, 1.16-1.20 (m CH_3), 2.15-2.35 (s Ar-H), 2.02 (m Ar-H), 7.30 – 7.43, 7.54 – 7.68, 7.71 – 7.83, 7.85 – 7.86, 8.09 – 8.12 (m Ar-H); ***CHN analysis calulated %***: C, 76.52; H, 5.12; N, 11.86; found C, 75.23; H, 5.08; N, 11.72. ***MS (m/z)***: 43, 76, 92, 119, 114, 159, 236.

(III-f) 3-Ethyl-2-methylquinazolin-4-(3H)-one:

UV: The absorption maxima at 259.20 nm in methanol. ***IR (KBr) cm^{-1}***, 1685.67, 3072.17, 2931, 2852, 1608.52; ***^{1}H NMR (300 MHz, DMSO-d$_6$)***, 1.12-1.42 (m CH_3), 2.49-2.60 (s Ar-H), 3.33-3.65 (s CH_2), 6.01 – 6.82 , 7.0 – 8.56, 1.97 – 2.22 (m Ar-H); ***CHN analysis calulated %***: C, 70.19; H, 6.40; N, 14.5; found C, 75.73; H, 6.40; N, 14.5. ***MS (m/z)***: 43, 74, 94, 116, 146, 162, 173, 188.

(III-g) 3-(3-Hydroxyphenyl)-2-methylquinazolin-4(3H)-one:

UV: The absorption maxima at 224.80 nm in methanol**.** ***IR (KBr) cm^{-1}***, 1680, 3034, 1598.88, 1608.42; ***^{1}H NMR (300 MHz, DMSO-d$_6$)***, 1.30 –1.31 (m CH_3), 3.33 – 3.65 (s CH_2), 2.14–2.30 (s Ar-H), 1.20 – 1.25 (m OH), 2.50 – 2.55 (m Ar-H), 6.80 – 6.82, 6.88 – 6.90, 7.30 – 7.36, 7.46 – 7.47, 7.49 – 7.51, 7.81- 7.84, 8.06 – 8.09 (m Ar-H); ***CHN analysis calulated %***: C, 71.98; H, 4.73; N, 10.76; found C, 75.98; H, 4.73; N, 10.76. ***MS (m/z)***: 47, 79, 97, 118, 147, 160, 174.

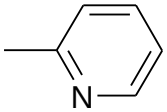
(III-h) 2, 3-Dimethylquinazolin-4-(3H)-one:

UV: The absorption maxima at 215.02 nm in methanol**.** ***IR (KBr) cm^{-1}***, 1683.74, 3064.68, 1604.66; ***^{1}H NMR (300 MHz, DMSO-d$_6$)***, 1.17 – 1.30 (m CH_3), 2.49 – 2.55, 3.20 – 3.65 (s Ar-H), 2.02 (m Ar-H), 6.01 – 7.06, 7.98 – 8.06 (m Ar-H); ***CHN analysis calulated %***: C, 68.95; H, 5.79; N, 16.08; found C, 68.25; H, 5.79; N, 16.12. **MS (m/z):** 45, 92, 142, 159, 235, 252.

RESULTS AND DISCUSSION

The purpose of this work was to synthesize various quinazoline **(III a - III h)** from the corresponding acids with great purity, high yields and environmentally friendly way. This was achieved with good success by the above described method. Consequently, from a green chemistry standpoint it is very important to develop a "green" system for chemical synthesizing. The product was proved as an ideal "green" quinazoline product due to its strength and lack of toxic by-products[20].

Quinazolin-4-(3H)-one analogues were prepared by the reaction between anthranilic acid, acid chloride and primary amine. To optimize the reaction conditions, the irradiation power, the reaction ratio and reaction time were variably investigated[21]. The reaction provided **III-c & III-g** with **89.70 % and 86.29%** yield after 10 min respectively at irradiation 560 W. In comparison, a conventional thermal heating of these types of reactions require 16-20 hrs with poor yield, 30-60 %. The reactivity of other primary amines towards was examined and the results are summarized in **Table 2.** The reaction may proceed via an unstable intermediate, 4-(3H)-benzoxazinone, as illustrated in general reaction which further reacts with primary amine to give the product.

Compound	R'	R"	Mol. Formula (Mol. wt)	Colour and shape	Melting point (^{0}C)	Yield (%)	R_f value*
III-a	$-CH_2CH_3$	Ph	$C_{16}H_{14}N_2O$ (250)	White crystals	110-112	84.50	0.32
III-b	Ph	Ph	$C_{20}H_{14}N_2O$ (298)	Yellowish orange ppt	123-125	82.80	0.35
III-c	Ph	Ph-OH	$C_{20}H_{14}O_2N_2$ (314)	White crystals	220-222	89.70	0.56
III-d	$-CH_2CH_3$		$C_{15}H_{13}N_3O$ (251)	White crystals	132-134	75.60	0.49
III-e	$-CH_3$	Ph	$C_{15}H_{12}N_2O$ (236)	White crystals	115-117	82.60	0.75
III-f	$-CH_3$	$-C_2H_5$	$C_{11}H_{12}N_2O$ (188)	Yellowish orange ppt	97-99	79.84	0.58
III-g	$-CH_3$	Ph-OH	$C_{15}H_{12}O_2N_2$ (252)	White crystals	226-228	86.29	0.68
III-h	$-CH_3$	$-CH_3$	$C_{10}H_{10}N_2O$ (174)	Yellowish orange ppt	102-104	77.30	0.62

*****Solvent system: ethyl acetate: n-hexane as mobile phase in the ratio of 3:7

Table 1. Physico-chemical data of quinazolin-4-(3H)-ones (III-a- III-h)

Compound **III-a** was synthesized in **84.50 %** yield after 09 min. of irradiation at 560 W while **III-b** & **III-e** was produced in **82.80% and 82.60%** yield after 10 min of irradiation at 560 W respectively**.** Moderate yield, **75.60%, 79.84%, 77.30% of III-d, III-f, III-h** was achieved in 10min when irradiated at 560 W. Increasing the amount of amine did not improve the yields significantly. The eight compounds listed in the tables **(III a - III h)** were screened for the antimicrobial activity against different bacteria and fungi.Method: Well diffusion method, Medium: the nutrient agar medium, Solvent: DMSO, Concentration: 10-30 g/mL. Conditions: 24 hrs to 7 days at 37 ^{0}C, Standard: the antibiotic Doxycycline and Fluconazole.

Biological activity studies

Antibacterial and antifungal activities

The antibacterial and antifungal activities were performed by cup plate method. Base layer was obtained by pouring about 10-15 ml of the base layer medium into each previously sterilized petri dish and were allowed to attain room temperature. The overnight grown subculture was mixed with seed layer medium, about 10-15 ml, was poured over the base layer and again allowed to attain room temperature[22]. The cups were made by scooping out agar with previously sterilized cork borer. The solutions of test compounds **(III a- III h)** were added in the cups by using pipettes. These plates were subsequently incubated at 37^{0}C for 48 hours. Inhibitory activity was measured (in mm) as the diameter of the observed inhibition zones for each organism. The tests were repeated to confirm the findings and average of the readings was taken intoconsideration[23]. The figures obtained are reported as the mean of three readings. Inhibition effects of quinazoline derivatives **(III a- III h)** on phytopathogenic bacteria and fungi were studied. The three bacteria, *S. aureus, P.aeuroginose, and E.coli* and two fungi, *C. albicans* and *A.niger* were collected and used in the bactericidal and fungicidal bioassays respectively. This screening was performed using 100 µg/ml and 150 µg/ml concentrations of the newly synthesized quinazoline **(III a-III h)** using Doxycycline as reference standard for antibacterial activity. Fluconazole was used as reference standard for antifungal activity and dimethylformamide (DMF) as a control for both the activities. Almost all the compounds **(III a-III h)** exhibited moderate inhibitory activity against the said species of organisms but none of them found to have any promising inhibitory activity. The data of antibacterial screening and data of antifungal screening is given in **Table 2**.

Compound	Bacteria and fungi along with zone of inhibition (mm)				
	S. Aureus **(ATCC-29213)**	***P. Aeruginosa*** ***(ATCC-10145)***	***E. Coli*** ***(ATCC-8739)***	***C. Albicans*** ***(ATCC-10231)***	***A. Niger*** **(ATCC-16404)**
III-a	**17.2**	**18.1**	**15.3**	**17.9**	**17.4**
III-b	**16.2**	**17.4**	**16.5**	**16.2**	**16.1**
III-c	**17.9**	**18.4**	**16.8**	**18.5**	**16.9**
III-d	**15.5**	**16.7**	**15**	**15.8**	**15.5**
III-e	**18.9**	**22**	**18.5**	**17.1**	**18.2**
III-f	**16.2**	**17.4**	**16.8**	**18.2**	**18.4**
III-g	**16.0**	**17**	**16.5**	**18.4**	**15.4**
III-h	**16.5**	**16.4**	**16**	**15.2**	**15.5**
Std-1 (Doxycycline)	**20**	**21.2**	**18.4**	**-**	**-**
Std-2 (Fluconazole)	**-**	**-**	**-**	**18.7**	**18.3**

Table 2. Biological Screening Data of synthesized Quinazolinone derivative

CONCLUSION

We have developed a convenient microwave assisted synthesis of 2, 3-disubstituted quinazolin-4-(3H)-ones (III-a to III-h). The method offers several advantages including good to high yields, cleaner products, a dramatic reduction in reaction time and an easy experimental work up procedure. Compound **III-e** had showed a better anti-microbial activity as compared to other analogues. The activity of compound **III-c, III-g and III-f** is comparable with that of fluconazole. From the data as shown in **Table 2**, it has been found that all the compounds tested showed broad spectrum of inhibitory properties. The compound **III-e** showed a good inhibition zone on pathogen *E.Coli* and moderate activity against the others. The rest of the compounds have moderate activity against all the tested pathogens. The method can be successfully used for the synthesis of some other analogues.

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REFERENCES:

1. Daniel L, Lednice G, Lester A, et al. The Organic Chemistry of Drug Synthesis, Wiley Interscience Publication, New York, 1977; 1:338-342
2. Seeley H.W, Denmark P.J.V, A Laboratory Manual of microbiology. Academic Press, New York, 1975, 2:55.
3. Daniel L, Lednicer G, Lester A, et al. The Organic Chemistry of Drug Synthesis, Wiley Interscience Publication, New York, 1980; 2:361.
4. Kashaw S, and Stables JP, Synthesis and CNS depressant activity of some derivatives of novel 3-[5-substituted-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazolin-4-(3H)-one. Eur. J. Med. Chem., 2007; xx:1-7.
5. Desai NC, Shah BR and Patel HH, anti HIV-1 activity of n- substituted aryl acetamides, Ind. J. of Chem, 1995; 34B:201-208.
6. Feng, Li, Feng Yi, et. al. An efficient construction of 2-[4-substituted-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazolin-4-(3H)-one under microwave irradiation. ARKIVOC, 2007, 1:40-50.
7. Lee Husing Kou, et. al. synthesis and biological evaluation of substituted 2- aryl quinazolinone, J. medi. Chem., 1994; 3:6-9.
8. Tyagi M, Pathak US and Rathod RS, synthesis of 3-monosubstituted quinazolin-4-(3H)-ones, Ind. J. of Chem, 1995, 2:617-623.

9. Thierry B. A., Jerome G. and Charles W. R., Multistep synthesis of thiazoloquinazolines under microwave irradiation in solution, Tetrahedron Letters, 41, (2000), 1027–1030.
10. Bahl BS and Bahl A, A Text Book of Organic Chemistry, S. Chand and Company Ltd. New Delhi, 1997; 14:735.
11. Sayed RE and AF, Wasfy, synthesis of heterocycles having double character: as antimicrobial, J. of Chinese chem. Soc, 2005; 52:129-135.
12. Guiry PJ, Connolly DJ and Cusack D, Synthesis of quinazolinones and quinazoline. Tetrahedron, 2005; 737:10153-202.
13. Feng Li, Meng Q and Feng Yi, an efficient construction of Quinazoline-4-(3H)-ones under microwave irradiation, ARKIVOC, 2007; (i): 40-50.
14. Meyyanathan S, ASEAN Review of biodiversity and environmental conversation (ARBEC), May 1998; 2:4-10.
15. Thierry BA, Jerome G, and Charles WR, Multistep synthesis of thiazoloquinazolines under microwave irradiation in solution, Tetrahedron Letters, 2000; 41:1027–1030.
16. Lidstrom P, Tierney J and Westman J, Microwave assisted organic synthesis- a review, Tetrahedron, 2001; 57:9225-9283.
17. Lottie B, and Thomas H, Microwave enhanced decarboxylation of aromatic carboxylic acid, improved potential, J. Chem. Research, 2000; 2:42-46.
18. Grover G and Kini SG, Synthesis and evaluation of new quinazolone derivatives of nalidixic acid as potential antibacterial and antifungal agents, Eur. J. Med. Chem., 2006; 41:256-262.
19. Wolfe FJ and Ashok kumar, synthesis of newer derivatives of 2- substituted derivatives of quinazolinone, J. Medi. Chem, 1990; 33:161-166.
20. Lee Husing Kou, synthesis and biological evaluation of substituted 2- aryl quinazolinone, J. medi. Chem, 1994; 54:203-205.
21. Bhrigu B, Pathak D, Siddiqui N, Alam MS and Ahsan W, "Search for biological active isatins: a short review." *Int J P'ceutical Sci & Drug Research* **2010**, 2(4), 229-235.
22. Swamy BN, Suma TK, Rao GV and Reddy GC "Synthesis of isonicotinoylhydrazones from anacardic acid and their in vitro activity against Mycobacterium smeg-matis." *Eur. J. Med. Chem*. **2007**, 42, 420–424.
23. Sriram D, Yogeeswari P, Basha JS, Radha DR, Nagaraja V, "Synthesis and antimycobacterial evaluation of various 7-substituted ciprofloxacin derivatives." *Bio-org. Med. Chem*. **2005**, 13, 5774–5778.