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IN SILICO CHARACTERIZATION, SYNTHESIS & PHARMACOLOGICAL SCREENING OF SOME NOVEL MALEMIDE DERIVATIVES FOR ANTIMICROBIAL ACTIVITY

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ABSTRACT

A major risk to human health is the specific rise in infectious diseases, especially in light of the opposition to modern antimicrobial medications. As a result, there is a global interest in discovering new antimicrobial medicines that are more effective when used just against bacteria strains that are resistant to all known antibiotics. Because it offers information for arranging molecules in order of importance for in vivo or in vitro assessments, in silico biological activity prediction is useful for drug discovery.

Maleimides have become significant pharmacophores in recent years and are essential medicinal agents with a variety of biological activities. Compounds from the maleimide series

were subjected to *in silico* biological activity predictions, partition coefficient (pLogP) calculations, and ADME calculations using the online programme. Melting point, TLC, 1H NMR, and IR spectroscopy were used in the synthesis and characterization of the series of compounds. Utilizing the agar disc diffusion method, the antimicrobial assessment of the studied compounds showed that Compounds (2d) and (2M) exhibit good antibacterial and antifungal activities among this series. Promising antibacterial and antifungal action was demonstrated by the remaining compounds.

Keywords: In silico, Maleimides, ADME Prediction, Antibacterial activity, Antifungal Activity

INTRODUCTION:

The majority of terrestrial biodiversity is made up of microorganisms (bacteria, fungus, protozoa), which are also essential to biosphere activities and frequently form biofilms on various surfaces **[19]**. As an illustration, bacteria have unique surface structures known as adhesins that can engage stereospecifically with receptors on the membrane of the host cell, just like lectins and carbohydrates or antigens and antibodies do **[15]**. Combining computer science, information science, and biology into one field is called bioinformatics **[20]**. It uses cutting-edge computational methods to organise and evaluate biological data. Maleic anhydride is converted into maleimide and its derivatives by treating it with amines and then dehydrating it **[1]**. Maleimides are particularly reactive because of their susceptibility to additions across the double bond, either through Diels-Alder reactions or Michael additions **[2]**. When maleic anhydride reacts with aromatic primary

"Performed on the computer or through computer simulation" is the definition of in silico. Pedro Miramontes coined the phrase "in silico." **[14]**. He conducted biological experiments, most of which were conducted on computers. for the generation of novel lead molecules. Maleimide is a particularly versatile heterocycle and considerable effort has been expended in the last 10 years in attaching the group to polymers **[17]**. By far the most prolific utilization of maleimide and its derivatives as pendant groups on polymers has been for the development of photosensitive materials **[18]**.

Chemistry of Maleimide:

amines to make the appropriate N-substituted maleamic acids, a number of N-substituted maleimides are produced **[1, 2]**. The corresponding maleimides were formed by dehydrating the produced maleamic acids with sodium acetate and acetic anhydride **[3]**. The appropriate maleimides were formed by dehydrating the obtained maleamic acids with

sodium acetate and acetic anhydride **[4]**. Maleimide also refers to a series of derivatives of the strong maleimide in which an alkyl or aryl group, such as methyl or phenyl, has been substituted for the NH group **[5]**. In the meantime, a maleimide moiety's vinylene group with a 1,2-disubstituted ethylene structure can copolymerize with vinyl acetate or polymerize with radical or anionic initiators to produce a polymer with excellent thermostability or heat resistance **[6, 7]**.

Biological activities and other uses of maleimide:

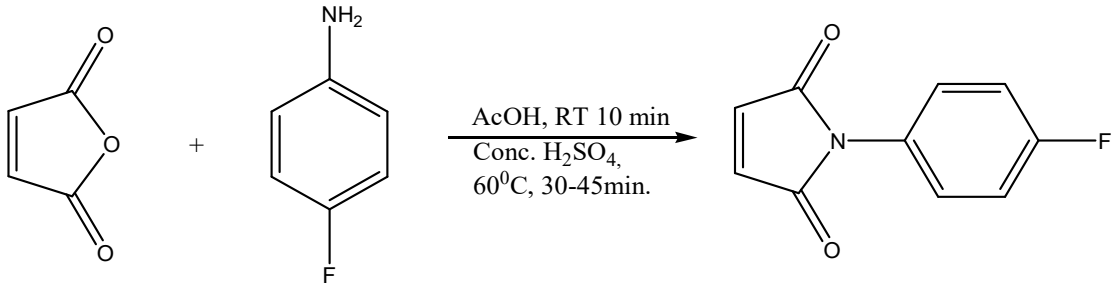
Maleimide compounds in particular have demonstrated analgesic, antifungal, and antibacterial qualities as well as the capacity to inhibit PKC and function as an antitumor **[8]**. The polymeric framework of several functional materials with exceptional heat stability is frequently made of polymaleimide (PMAI), a highly reactive polymer **[9]**. Maleimides are crucial medicinal agents with a variety of biological activities, including antibacterial, analgesic, antistress, antiprotozoal, antiangiogenic, cytotoxic, DNA binding, and apoptosis inducing activity **[10]**. For instance, Polymaleimide was used to prepare nonlinear optical materials as liquid crystals to improve their thermal properties **[13]**.

MATERIAL AND METHODS

All the chemicals and solvents used were purchased from commercial sources and were of high purity. Melting points were taken in open glass capillary Thieles Tube. Thin layer chromatography was done with silica gel G. TLC Monitoring done by Following Solvent System as Mobile Phase Hexane: Ethyl acetate (2:1); Hexane: Ethyl acetate (6:4). The spots were detected by exposure to iodine vapors and UV cabinet. Infra-red spectra of compounds were recorded on Bruker ATR, software OPUS. Proton 1H Nuclear Magnetic Resonance spectra of compounds were recorded on Bruker DPX 400 MHz NMR Instrument using solvent DMSO.

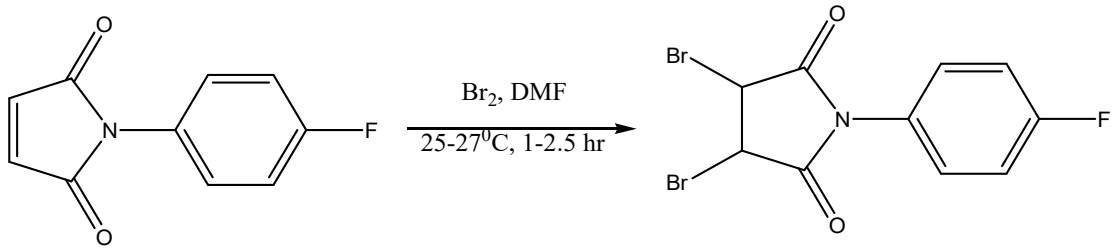
SYNTHESIS

Step 1: Synthesis of N-(p-fluorophenyl) maleimide [1d]



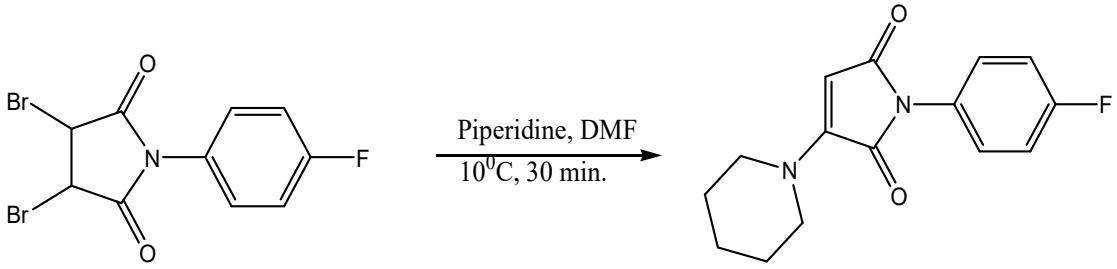
To a vigorously stirred (stir bar) solution of the amine (0.04 mole) in acetic acid (30 ml), the anhydride (0.044 mole) was added in one lot. The reaction mixture was stirred further for 10 minutes at room temperature. The clear solution turned into slurry due to separation of the amic acid. To this stirred slurry, concentrated sulfuric acid (9.20 g, 0.0938 mole) was added in one lot. Due to the exothermic reaction, temperature increased by 10 to 15◦C and the suspension turned into a clear solution. The temperature of reaction mixture was then maintained at 60◦C for 30–45 minutes. The cooled reaction mixture was poured onto crushed ice (100 g). The solid separated was collected, washed with aqueous sodium bicarbonate and then with water, and recrystallized from aqueous ethanol.

Step 2: Synthesis of 3,4-dibromo-N-(p-fluorophenyl) succinimide [2d]



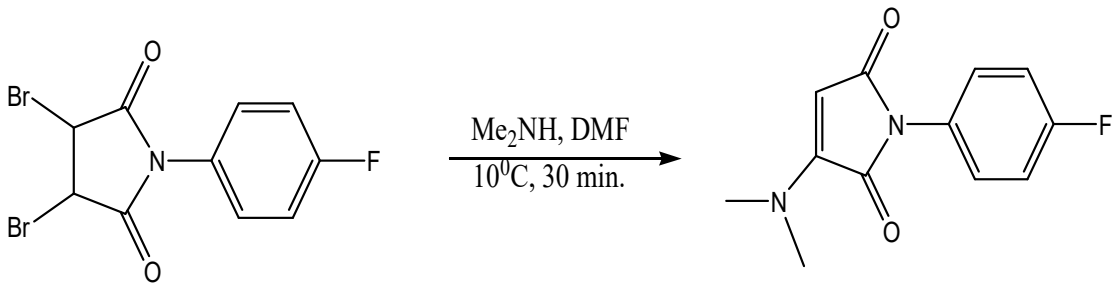
To a solution of N-aryl maleimide **1(d)** (1 mmol) in DMF (3 mL) was added dropwise a solution of bromine (1 mmol) in DMF (2 mL) at 25°C and stirred further for 1 to 2.5 hr (TLC, hexane:ethyl acetate, 2:1). The reaction mixture was poured onto crushed ice. The precipitated white solid was filtered, washed with cold water, dried and purified by recrystallization using ethanol.

Step 3: Synthesis of 3-piperidino-N-(p-fluorophenyl) maleimide 3(J)



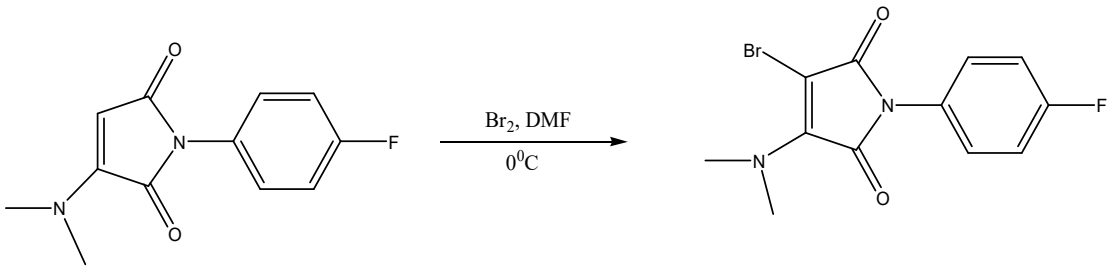
To a solution of trans-3,4-dibromo-N-arylsuccinimide **2(d)** (1 mmol) in DMF (5 mL), secondary amine (3 mmol) was added dropwise at 10°C and stirred for 10 min. The reaction mixture was poured over crushed ice. The precipitated golden yellow solid was filtered, washed with cold water, dried.

Step 4: Synthesis of 3-dimethyl amino-N-(p-fluorophenyl) maleimide 6(Y)



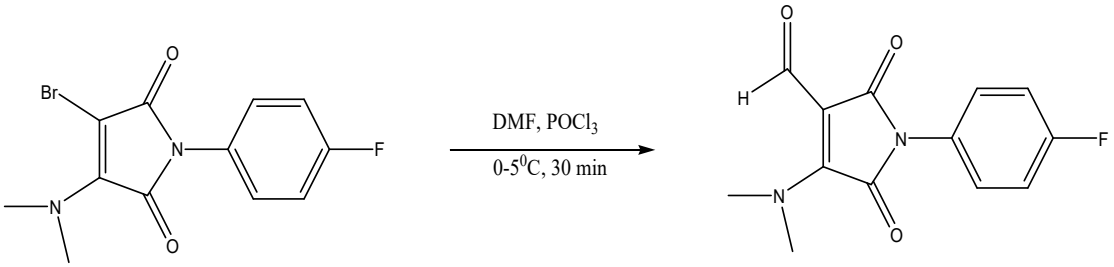
To a solution of trans-3,4-dibromo-N-arylsuccinimide **2(d)** (1 mmol) in DMF (5 mL), secondary amine (3 mmol) was added dropwise at 10°C and stirred for 10 min. The reaction mixture was poured over crushed ice. The precipitated golden yellow solid was filtered, washed with cold water, dried.

Step 5: Synthesis of 3-dimethyl amino, 4-bromo-N-(p-fluorophenyl) maleimide 7(Y)



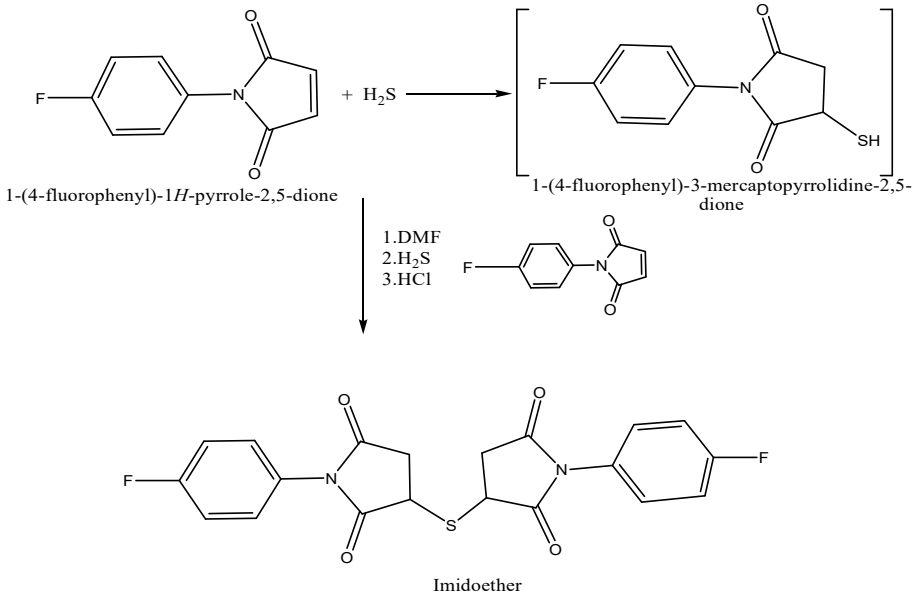
To a solution of 3-dialkylamino-N-arylmaleimide 6(y) (1 mmol) in DMF (3 mL) was added dropwise a solution of bromine (1 mmol) in DMF (2 mL) at 0°C. After addition of bromine, the reaction mixture was poured over crushed ice. The precipitated yellow solid was filtered, washed with cold water, dried.

Step 6: Synthesis of 4-(dimethylamino)-1-(4-fluorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carbaldehyde 8(Y)



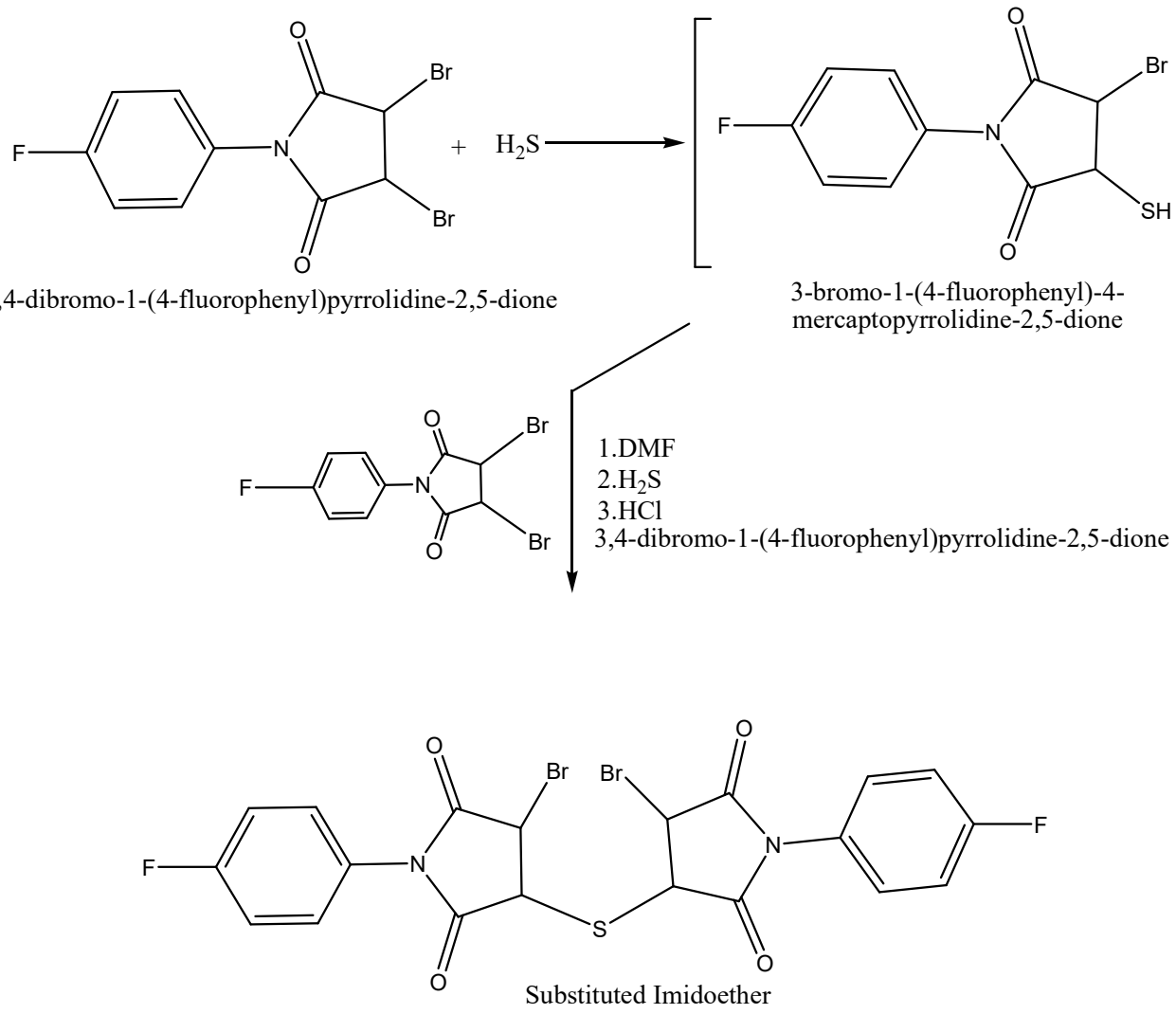
To a Vilsmeier-Haack adduct prepared from DMF (3 mL) and POCl3 (1.2 mmol) at 0°C was added 6(y) (1 mmol) and stirred at 0-5°C for 30 min. The reaction mixture was poured into cold water. The yellow solid was separated on neutralization with 10% aqueous NaHCO3 solution, was filtered, washed with cold water, dried and purified by column chromatography (hexane:ethyl acetate, 6:4).

Step-7: Synthesis of Imidothioether (1M)



A mixture of 8.65 g (0.05 mole) N-(p-fluorophenyl) maleimide 1(d) and 25 ml DMF was placed in a 150-ml flask, and a slow stream of H_2S was bubbled into the solution. Reaction occurred rapidly, and the temperature rose to 6O^{O}C. The color of the reaction mixture changed from yellow to orange. Isolation of the product was achieved by pouring the entire reaction mixture into water containing several drops concentrated HCl. The nearly white product was filtered and dried.

Step-8: Synthesis of substituted Imidothioether (2M)



A mixture of 8.65 g (0.05 mole) 3,4-dibromo-N-(p-fluorophenyl) succinimide **2(d)** and 25 ml DMF was placed in a 150-ml flask, and a slow stream of H_2S was bubbled into the solution. Reaction occurred rapidly, and the temperature rose to $60^{O}C$. The color of the reaction mixture changed from yellow to orange. Isolation of the product was achieved by pouring the entire reaction mixture into water containing several drops concentrated HCl. The nearly white product was filtered and dried.

Table 1: Physical characterization of synthesized Compound

Compound code	Molecular formula	Molecular weight	Yield (%)	Melting point (°C)	Rf
1d	$C_{10}H_6FNO_2$	190	73%	200-205	0.583
2d	$C_{10}H_6Br_2FNO_2$	348	77%	165-170	0.705
3J	$C_{15}H_{15}FN_2O_2$	274	73%	190-195	0.558
6Y	$C_{12}H_{11}FN_2O_2$	234	86%	140-145	0.636
7Y	$C_{12}H_{10}BrFN_2O_2$	313	90%	195-200	0.666
8Y	$C_{13}H_{11}FN_2O_3$	262	79%	160-165	0.576
1M	$C_{20}H_{14}F_2N_2O_4S$	416	82%	260-265	0.62
2M	$C_{20}H_{12}Br_2F_2N_2O_2S$	542.19	87%	275-280	0.58

Table 2: Spectral Analysis of synthesized compound

Compound Code	MW	Rotatable bonds	H-bond acceptors	H-bond donors	M LOGP	Lipinski #violations
1d	191.16	1	3	0	1.53	0
2d	348.95	1	3	0	2.36	0
3J	274.29	2	3	0	2.02	0
6Y	234.23	2	3	0	1.65	0
7Y	313.12	2	3	0	2.04	0
8Y	262.24	3	4	0	1.00	0
1M	416.40	4	6	0	3.11	0
2M	574.19	4	6	0	3.76	1

Table 3: Lipinski's Rule of Five (Ro5)

Sr. No.	Compound Code	IR Values (cm^{-1})	^1H NMR Values (δ ppm)
1.	1d $C_{10}H_6FNO_2$	3409, 1700, 1143, 834, 683.	7.38-7.39 (HA) , 7.39-7.41 (HB) , 7.32-7.33 (HC)
2.	2d $C_{10}H_6Br_2FNO_2$	3432, 1659, 1146, 830, 762, 675.	5.54-5.55 (HA) , 7.393-7.399 (HB) 6.29-6.30 (HC)
3.	3J $C_{15}H_{15}FN_2O_2$	3416,1667,1150,847,764.	1.46 -1.71(HA), 3.20 - 5.79 (HB), 7.08 - 7.54 (HC)
4.	6Y $C_{12}H_{11}FN_2O_2$	3236,1704, 1146, 833, 688.	5.79 (HA) , 7.39 (HB) , 6.64-6.66 (HC), 2.50-2.55 (HD)
5.	7Y $C_{12}H_{10}BrFN_2O_2$	3235, 1704, 1141, 831, 686.	7.64 (HA), 6.32-6.47 (HB), 1.23-1.24 (HC)
6.	8Y $C_{13}H_{11}FN_2O_3$	3099, 1708, 1147, 832, 682.	10.44 (HA), 7.64 (HB), 6.45-6.47 (HC), 1.23 (HD)
7.	1M $C_{20}H_{14}F_2N_2O_4S$	3392,1709,1504, 1387, 1229,835	2.82-3.06(HA), 4.69-4.82(HB), 7.03-7.16(HC), 7.49-7.61(HD)
8.	2M $C_{20}H_{12}Br_2F_2N_2O_2S$	3463,1710,1653,1501,1218, 828	4.82- 5.45(HA), 7.10 - 7.55 (HB) 8.4 (HC)

ADME characterization of compound

Physicochemical properties of new compounds obtained using the SWISSADME server.

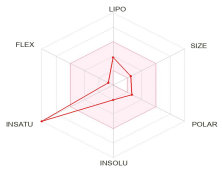
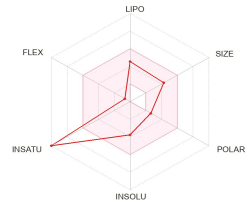
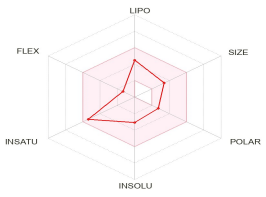
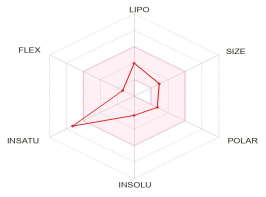
Table 4: Pharmacokinetics Parameters

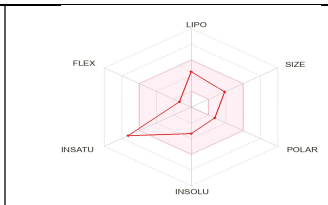
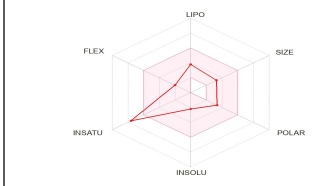
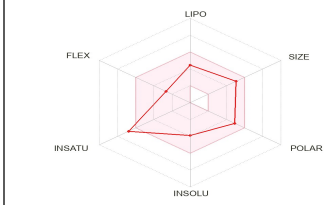
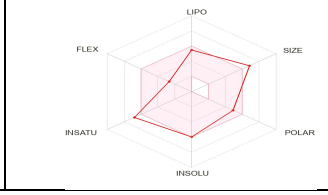
Compound Code	TPSA	GI absorption	BBB permeation	Pgp substrate	Bioavailability Score
1d	37.38	High	Yes	No	0.55
2d	37.38	High	Yes	No	0.55
3J	40.62	High	Yes	No	0.55
6Y	40.62	High	Yes	No	0.55
7Y	40.62	High	Yes	No	0.55
8Y	57.69	High	Yes	No	0.55
1M	100.06	High	No	No	0.55
2M	100.06	High	No	No	0.55

Bioavailability Radar

The ideal range for each attribute is shown by the pink area. Lipophilicity: XLOGP3 in the range of -0.7 to +5.0, Dimensions: MW 150–500 g/mol, TPSA polarity ranges from 20 to 130 Å2. Solubility: no log S greater than 6. Saturation is defined as having at least 0.25 percent of the carbons in the sp3 hybridization. Maximum flexibility: nine rotatable bonds.

Table 5: Bioavailability Radar & Remark

Compound Code	Bioavailability radar	Remark
1d		The image shows that Compound 1d doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.
2d		The image shows that Compound 2d doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.
3J		The image shows that Compound 3J fits in the pink-shaded region, meaning it is orally bioavailable.
6Y		The image shows that Compound 6Y doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.

7Y		**The image shows that Compound 7Y doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.**
8Y		**The image shows that Compound 8Y doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.**
1M		**The image shows that Compound 1M doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.**
2M		**The image shows that Compound 2M doesn't fit in the pink-shaded region, meaning it is not orally bioavailable.**

BOILED-Egg for Prediction of GI Absorption and Brain Penetration:

Additionally, the blood-brain barrier (BBB) permeation and passive human gastrointestinal absorption (HIA) were among the parameters of the ADME that were predicted in vivo using the graphical categorization model, the Egan BOILED-Egg (Brain Or IntestinaL Estimated) permeation predictive model diagram. BBB permeability is present in compounds 1d, 2d, 3J, 6Y, 7Y, and 8Y.

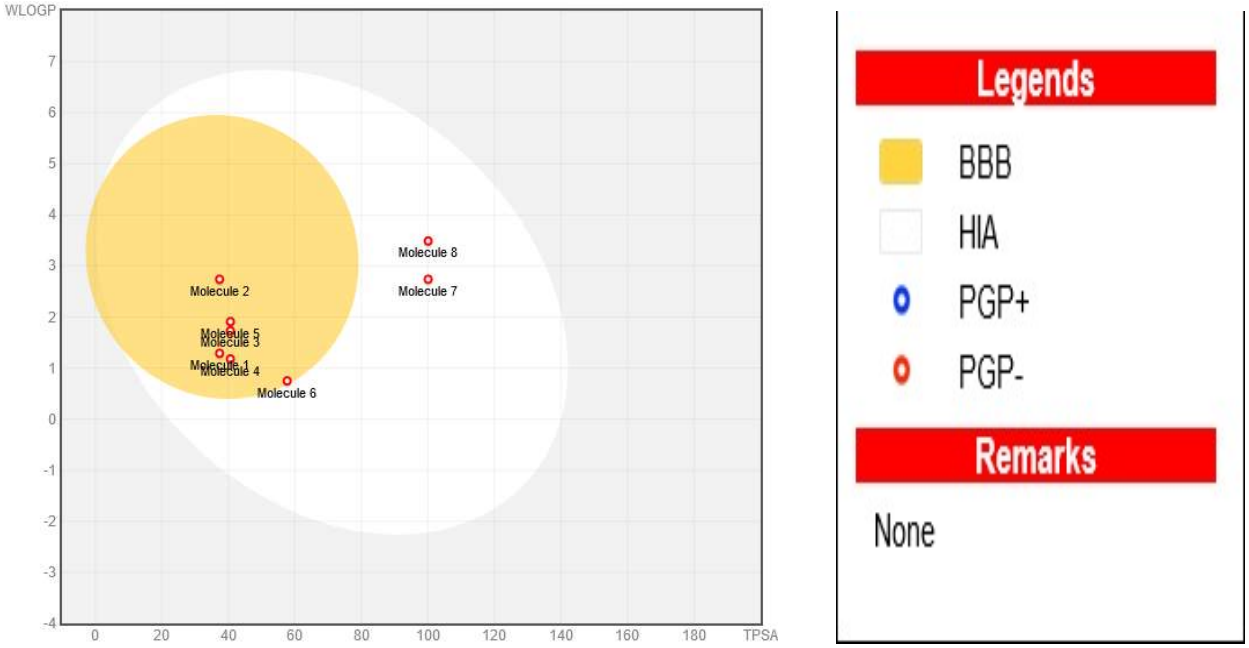


Figure 1: Boiled Egg Diagram from SWISS ADME

Antimicrobial activity

The disc diffusion method was utilized to assess the antibacterial activity of the synthesized compounds against the strains of *E. coli*, *P. aureus, S. aureus,* and *Candida*. Positive controls against fungi and bacteria were gentamycin and nystatin, respectively. The discs were incubated at 370C for 14 days in order to determine the zone of inhibition **(Table 5)**. Following the identification of the zone of inhibition and comparison with the reference medication, the compounds were assessed. As per **Table 4**, solutions for 1d, 2d, 3J, 6y, 7y, 8y, 1M, and 2M are prepared.

Table 6: Compound and their concentrations used for activity

Compound Code	Weighed quantity of compound	Weighed volume of solvent	Conc. In mg/ml
1d	20mg	0.5 ml	40
2d	20mg	0.5 ml	40
3J	20mg	0.5 ml	40
6y	20mg	0.5 ml	40
7y	20mg	0.5 ml	40
8y	20mg	0.5 ml	40
1M	20mg	0.5 ml	40
2M	20mg	0.5 ml	40

Table 7: Compound and their zone of inhibition

Sample No.	*E. coli* ATCC 25922	Pseudomonas Aeruginosa ATCC27853	Staphylococcus Aureus ATCC 25923	Candida sp.
1 (d)	09 mm.	No zone	16 mm.	18 mm.
2 (d)	13 mm.	No zone	19 mm.	20 mm.
1 (M)	No zone	No zone	13 mm.	14 mm.
2 (M)	11 mm.	07 mm.	17 mm.	19 mm.
3 (J)	No zone	No zone	10 mm.	15 mm.
6 (Y)	08 mm.	No zone	16 mm.	18 mm.
7 (Y)	07 mm.	No zone	13 mm.	15 mm.
8 (Y)	07 mm.	No zone	16 mm.	15 mm.
Gentamicin	17 mm.	21 mm.	25 mm.	--
Nystatin	--	--	--	21 mm

RESULT AND DISCUSSION:

A series of substituted N-(p-fluorophenyl) maleimide derivatives were successfully synthesized, and the structures of the synthesized compounds were confirmed by chromatographic and spectral analysis. An insilico study of the compound revealed that a synthesized compound show significant result for Log P, BBB, TPSA, and ADME. It was discovered that the substituted N-(p-fluorophenyl) maleimides that were synthesized were pure, had a good yield, and had repeatable outcomes. The accompanying table no. 07 shows the findings of investigations on the antibacterial and antifungal properties of all the produced compounds. Among this series, compound (2d) exhibits encouraging antibacterial and antifungal action. It demonstrated strong antibacterial and antifungal properties against Gram-positive and Gram-negative bacteria, respectively (*E. coli* at 40 mg/mL and S. aureus at 40 mg/mL). Species of Candida at 40 mg/mL. When compared to the standard antibacterial drug Gentamycin, Compound 2M exhibits better antibacterial activity against Gram-negative bacteria (*E. coli* at 40 mg/mL and P. aeruginosa at 40 mg/mL) and Gram-positive bacteria (S. aureus at 40 mg/mL). It also demonstrates good antifungal activity against Candida species at 40 mg/mL when compared to the standard antifungal drug Nystatin. Similar to this, further maleimide derivatives (1d, 6Y) demonstrated detectable efficacy against both Gram-positive and Gram-negative bacteria (*E. coli* at 40 mg/mL and S. aureus at 40 mg/mL).In comparison to the standard antibacterial drug Gentamycin, the remaining compounds (1M, 3J, 7Y, and 8Y) exhibit less antibacterial activity against Gram-negative bacteria (*E. coli* at 20 mg/mL, P. aeruginosa at 40 mg/mL, and Gram-positive bacteria (S. aureus at 40 mg/mL) and less antifungal activity against Candida species at 40 mg/ml.

CONCLUSION

In conclusion, the class of recently synthesized derivatives of maleimide shows promise as antifungal and antibacterial agents. Of this series, compound (2d) exhibits encouraging antibacterial and antifungal action. It shown strong antibacterial and antifungal properties against Candida species at 40 mg/mL and Gram-positive and Gram-negative bacteria (*E. coli* and S. aureus, respectively) at 40 mg/mL. The examined substances have good oral bioavailability and membrane permeability, with typically high absorption in the gastrointestinal tract, according to the findings of the in silico research. In summary, the findings validate the novel maleimide derivatives' multidirectional antibacterial activity and demonstrate how structural substitution influences this class of drugs' ability to combat various microorganisms. With the disc diffusion approach, the antibacterial activity is ascertained. The compounds (2d) and (2M) in this class exhibit good antibacterial and antifungal action. The remaining substances exhibited encouraging antifungal and antibacterial properties.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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